Hormonal Contraception Osteoporosis

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Case study – Hormonal contraception

Patient: woman, 35 years, non-smoker, BMI 26, she has three children

- BP 118/75
- **Family history**: no risk factors in the family described
- **Personal history:** depression
- **Medicine history:** ethinyloestradiol 35 mg/norethisterone 1 mg + citalopram 10mg 1 - 0 - 0
- She comes for an advice. She started taking oral contraceptives (COCPs) six months ago. Since then, at time of weekly intervals without contraception she always suffered from severe headaches - migraine without aura

1. Case study – Hormonal contraception

Tasks:

1. How does the female hormonal contraception work, which hormones are involved and how they change during the period?

Synthetic **estrogen** in the pill works to - **NEGATIVE FEEDBACK**

- Stop the pituitary gland (hypohysis) from producing **follicle stimulating hormone** (FSH) and luteinizing hormone (LH) in order to **prevent ovulation**
- Support the uterine lining (endometrium) to **prevent breakthrough bleeding** mid-cycle.

Synthetic **progestin** works to:

- Stop the pituitary gland from **producing LH** in order to **prevent egg release**
- Make the **uterine lining** inhospitable to a fertilized egg.
- Partially limit the sperm's ability to fertilize the egg
- Thicken the **cervical mucus** to hinder sperm movement (although this effect may not be key to preventing pregnancy).

Case study – Hormonal contraception

Tasks:

2. What types of **oral** hormonal contraception exist and how do they work?

- **Progestines/combined**
  - Monophasic - one hormone dose over a cycle
  - Biphasic - two hormone doses over a cycle
  - Triphasic - three hormone doses over a cycle

3. Make an analysis of prescription, give active substance, ATC classification, describe the mechanism of action of individual preparations, check the dosage and method of use (morning / evening, before / after meals, etc.)

1. Combined oral contraception

Starting a Regimen

- combination pill—contains both estrogen and progestin—within 5 days after the beginning of your menstrual period - protected from pregnancy immediately

Day-to-Day Use

- Combination pills **most often come in a 21-day or 28-day pack** (the package comes with seven reminder pills, sometimes called placebos, which contain no active ingredients and are only meant to help you stay on track.
- When taking the **21-day form**, you will simply not take pills during the last week of your cycle, during which you will have your period.

Keeping a Schedule

- It's best to take your pill at the same time each day to maximize efficacy. This way, your body will get used to receiving a hormonal boost regularly - along with a morning routine such as brushing your teeth or putting on your makeup.
- If you miss a day, it increases your chances of becoming pregnant. With the progestin-only pill, it is essential to take it at the same time each day.
- If you confirm that you are pregnant, stop taking the pill.

2. Citalopram

- should be administered in a single oral daily dose of 20 mg. Depending on the patient's individual response, the dose can be increased up to a **maximum daily dose of 40 mg** (or decreased)?

Duration of therapy

- An antidepressant effect usually occurs after **2-4 weeks of treatment**
- Treatment is symptomatic and must be prolonged for a reasonable time, usually 6 months after withdrawal of the symptoms, to avoid relapse
- There is **no effect of food** on the absorption
- Citalopram has little or moderate influence on the ability to drive

Side effects:

- drowsiness, nausea, insomnia, and diaphoresis, ejaculatory disorder
- suicidal tendencies, agitation, diarrhea, anxiety, confusion, exacerbation of depression, lack of concentration, tremor, vomiting, anorexia, and xerostomia

Case study – Hormonal contraception

4. Find the **potential interactions** between agents. How can hormonal contraception interact with certain antidepressants? What is the possible mechanism of this interaction?

IT ethinylestradiol / norethisterone and citalopram:

- **CYP450, 3A4** - there is not a problem with citalopram (it is metabolized through both CYP2D6 and CYP3A4, so one isoenzyme blockade does not matter
- definitely not to recommend sertraline, it has the highest incidence of premenstrual depressive dysphoria (3-8% of women)
- theoretically, there is an **increased risk of bleeding** (ADR of all SSRIs) - due to platelet reuptake of serotonin, thrombocytes - less activity
- Another problem is in the patient's migraine. Tramadol (risk of serotonin syndrome) is not considered, for triptans it is possible with SSRI with caution, it is not recommended.

Case study – Hormonal contraception

5. Is there an association between the use of contraception and headaches? What **side effects** are likely to occur in patients receiving hormonal contraception?

- Irregular cycle (wait 3-5 cycles)
- Weight gain
- Tension in the breast
- Headaches
- Changes in mood, libido disorders ????
- Vaginal discomfort (vaginal inserts with progestines)

6. Is it necessary to replace the current hormonal contraception with another, more appropriate for this patient, or to continue the current?

7. What type of contraception would recommend to take this patient? What options (dosage forms, products) contraception, oral is available?

Case study – Hormonal contraception

Contraindications of COCPs

- history of deep vein thrombosis or embolism
- demonstrated thrombophilic status
- history of hormonal dependent tumors (breast cancer, endometrium, ovarian endometrioid carcinoma and uterine sarcoma)
- acute and chronic liver disease with impairment of function (except for Gilbert's disease), untreated or untreated hypertension and primary pulmonary hypertension or multiple family history of thrombosis

Contraindocations relative

- **migraines with aura**
- diabetes mellitus with vascular changes
- severe prolapse of the mitral valve and other heart defects with a high risk of embolism
- smoking in women over 35 years of age
- severe dyslipidemia

Case study – Hormonal contraception

Migraine without aura **progestine-only contraception**

Progestines:

- **KI absolute** - only pregnancy and breast cancer

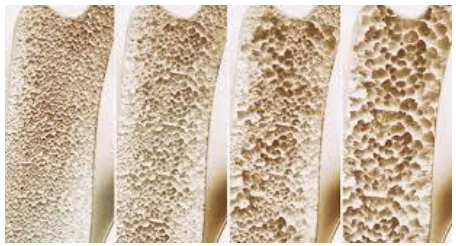
- **Relative** – ictus, schemic heart disease, **acute** VTE, liver, depression, osteoporosis risks
- Also suitable for **higher risk of VTE,** hypertension, heart defects, vascular migraine, DM, stroke intolerance, smokers older than 35 years and nursing women

Tabulka 5. Preparáty gestagenní kontracepce

Název	Složení	Forma
Cerazette	desogestrel 75 µg	28 tablet
Depo-Provera 150 mg/ml	medroxyprogesteron acetát 150mg v 1 ml	injekce
Mirena	levonorgestrel 52 mg	nitroděložní tělísko

2. Case study - Osteoporosis

- **Patient:** Renata, age 42 years old, smokes 10 cigarettes a day, drink 3 cups of coffee a day, sometimes alcohol - wine
- **Laboratory values:** height 161 cm, weight 54 kg, BP 125/70
- **Personal history:** Depo-Provera as a contraceptive used, currently osteoporosis was diagnosed
- **Drug history:** Depo-Provera 1 month



Case study - Osteoporosis

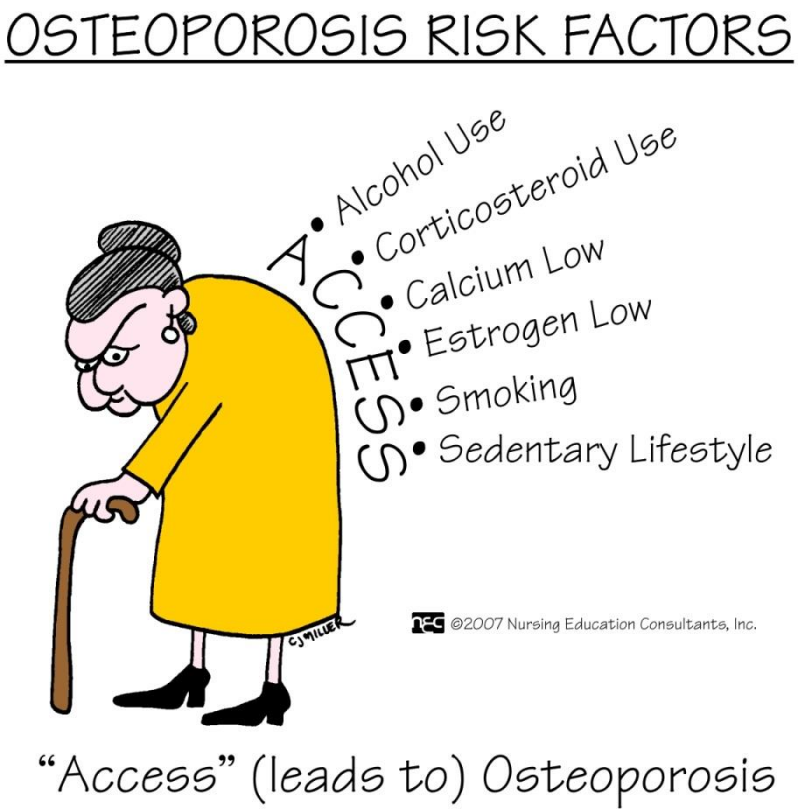
Tasks:

1. What is osteoporosis? What is the prevalence?

- **7-8%** of the population - "civilization disease"
- World prevalence of **200 million people** (Czech Rep. 200.000/800.000)
- ¾ patients undiagnosed (or poorly treated)!!!
- The **osteoporotic fracture** is threatened by every 3th woman and every 5th over age 50
- The fracture of the femoral neck represents a **high mortality rate and the highest incidence of invalidation** (by 2050 assumption of an increase of 310/240%)

Case study - Osteoporosis

2. What are the common risk factors for osteoporosis? What risk factors can be found in this patient?



Case study - Osteoporosis

3. How is osteoporosis treated? Describe all types of treatment (pharmacological, physiotherapy, alternative treatment, …). Which group of medicines are used for the treatment of osteoporosis? What are their main advantages / disadvantages?

Terapie osteoporózy

- Zmírnění bolesti ~~(kalcitonin)~~
- **Výživa**
- **Cvičení a fyzioterapie**
- Suplementace **kalcia a vitamínu D**
- **Medikamentózní léčba**
- Ortézy, bederní pásy
- Operační léčba
- Sociální podpora
- Aktivní spolupráce pacienta!!!

4 hod/den

Pharmacological treatment

Inhibition of bone resorption

- Estrogens
- Bisphosphonates
- (Calcitonin)
- SERM - raloxifene
- Strontium ranelate
- Calcium
- Denosumab

anti-resorptive therapies-bisphosphonates with the amino group in the side chain

Stimulation of bone formation

- Vitamin D
- Anabolika Teriparatid
- Strontium ranelate
- Osteogenon
  - organic elements of bone (ossein) and microcrystalline hydroxyapatite) containing calcium and phosphorus
  - In ossin protein and non-protein substances with a positive effect on the formation of bone tissue.

Case study - Osteoporosis

4. Is Depo-Provera ideal contraceptive for this patient? Would you possibly suggest any changes and why?

5. Which treatment of osteoporosis you would recommend for this patient ? Suggest specific medications, frequency of dosing, patient counselling.

6. What regime and non-pharmacological measures would you recommend to the patient for optimal treatment of osteoporosis? (nutrition, physical activity, …).

Hormonal contraception

Which contraceptives are most effective?

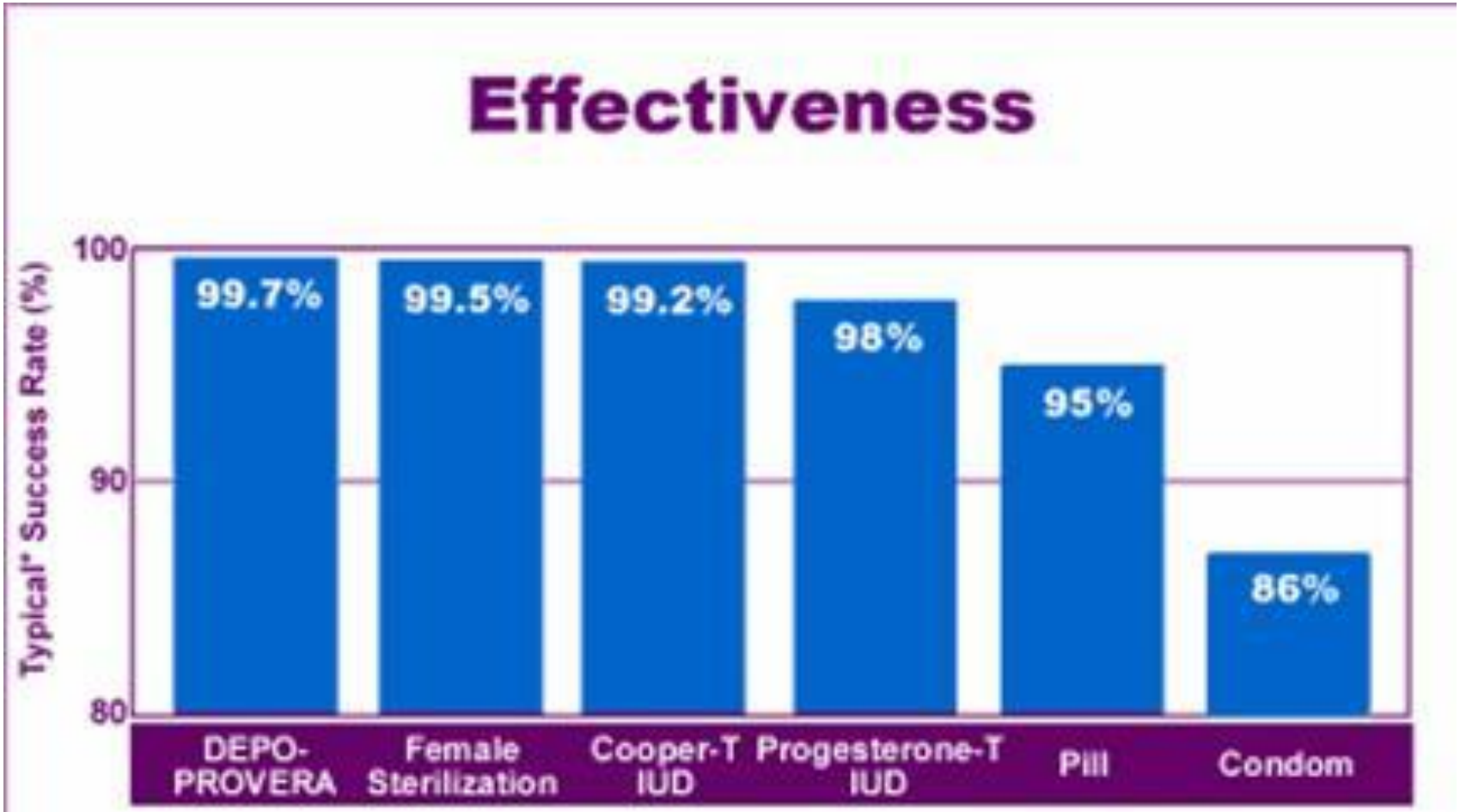
Which can we recommend which woman?

Pearl index – contraceptive **effectiveness**

(Failure per 100 females per 1 year)

Unprotected sexual intercourse	80 - 85
Spermicides (local contraceptives)	0.1 - 25
Condom (prophylactic)	14
Combined HAK	0.1 - 0.4
Oral gestagens	0.14 - 9.60
Depot gestagens	0.00 - 1.0
IUD - Cu	0.2 - 0.8
IUD – levonorgestrel	0.02 - 0.2

The effectiveness of contraception



Adapted from Trussell, Kowal.[1] *"Typical" includes those not following directions exactly.

Reference: 1. Trussell J. Kowal D. The essentials of contraception: efficacy, safety, and personal considerations. In: Hatcher RA, Trussell J, Stewart F, et al. Contraceptive Technology. 17th rev ed. New York, NY: Ardent Media; 1998:211-247

1. Local contraceptives

What is it?

How do they work?

How are they used?

Who are they suitable for?

1. Local contraceptives

Mechanism of action:

Destruction of sperm membranes

Use: 5 - 10 minutes before sex act, leave 6 hours after contact, **do not wash**!

Do not use alkaline soaps for intimate hygiene.

(Nonoxinolum - Patentex oval)

Benzalkonium chloride - **Pharmatex vag. glo., vag.crm.**

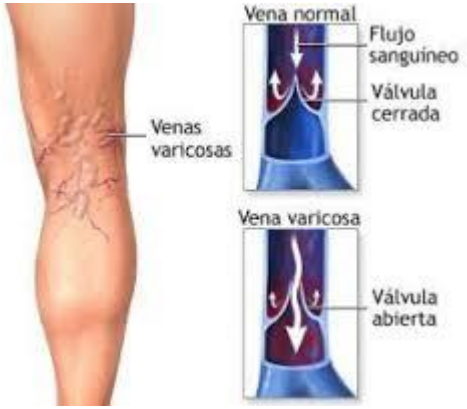
Pharmatex vag glo, gel (260,- Kč)

- **Intimate parts of body wash** 2 hours before and 2 hours after contact - **only with warm water** (due to possible chemical reaction of the detergent with Pharmatex)

- The most risky is contact with classic (solid) soap, but beware of shower gels…. it applies to both partners, after contact only for a partner (unless you want to continue sex later).
- **Pharmatex** has an antiseptic effect, so it protects most microorganisms. And if you have a permanent partner, you do not have to worry.

For which woman are local contraceptives appropriate?

- Young girl
- Breeding mother
- Premenopausal woman
- Woman treated for varicose
- Smoker
- After a thromboembolic event



- A woman with intermittent (not regular) sexual intercourses
- A woman with high liver tests
- In addition, women who forget to take a contraceptive tablet may use it as an occasional way of protecting them.

2. Progestin contraceptives

What is it?

What is the mechanism of action?

How are the rules of use?

What types do we know?

Which women are suitable for?

2. Progestin contraceptives

- It contains **only progestin** (…desogestrel) – p.o. **Cerazette, Azalia**
- MA: **suppress** ovulation in only 70% of cases, thicken cervical mucus, suppress endometrial proliferation, reduce motility of oviductes

Suitable for:

- nursing mothers
- women suffering from migraines
- women who can not take estrogen
  - VTE of a history
  - Hypertension
  - Heart diseases
  - DM
  - Smokers older than 35 years

Progestin contraceptives

- They are used continuously (28tbl), not a normal 7-day pause, exactly **at the same time of day**
- Apply the **missed dose** immediately with the use of barrier protection in the next 7 days
- 1. choice in breast-feeding women (6 weeks after birth = puerperium)

Tabulka 5. Preparáty gestagenní kontracepce

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Progestin contraceptives

- It is necessary to **use it regularly** (after a period of more than **3 hours** - possibility of failure)
- For users **weighing more than 70kg**, the risk of failure also increases

- **ADE:** irregular bleeding (cycle) amenorrhea, acne, hirsutism, headaches, ...

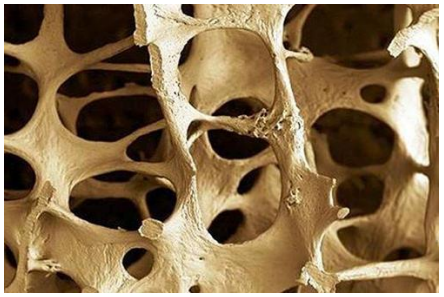
- **Interactions** - when using acetylcysteine containing **mucolytics** at **higher doses than recommended** (more than 600mg / day), it can affect the permeability of the cervical mucus and thereby reduce the effect

Progestin-only pills (POPs)

- Side effects
  - Headache
  - Breast tenderness
  - Acne/Hirsutism
  - Nausea
  - Spotting
- Contraindications
  - Known or suspected pregnancy
  - Genital bleeding of unknown etiology
  - Liver tumors
  - Acute liver disease

Depot progestins

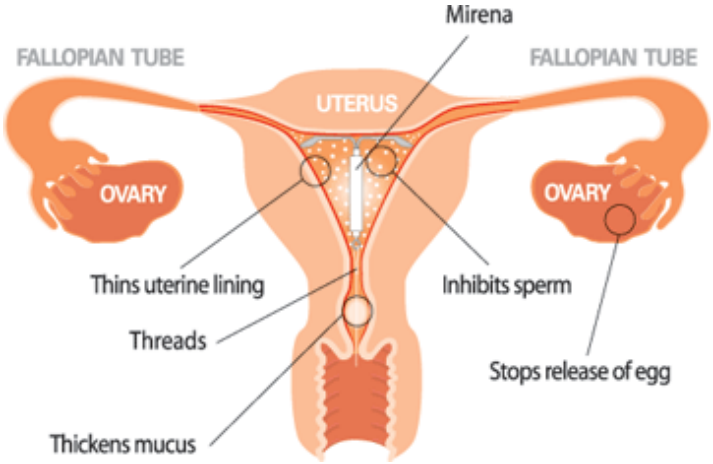
- Depot medroxyprogesterone acetate
- (i.m. Depo-provera., s.c. Sayana)
- Patients with **low adherence** to treatment
- Injection each 14 weeks (3 moths)
- **Amenorrhea** in 1/3 of patients in the first 3 months
- Loss of bone mineral - decrease in bone density
- Fertility is restored in 10-18 months



IUD with levonorgestrel (Mirena)

(intrauterine device)

- The most reliable reversible contraception
- 0.02mg of levonorgestrel **for 5 years**
- For women who have already given birth
- With monogamous partner, they want **long-term contraception**
- Apply in the first 7 days of menstrual bleeding
- Risk of inflammation only during the first 20 days after implementation

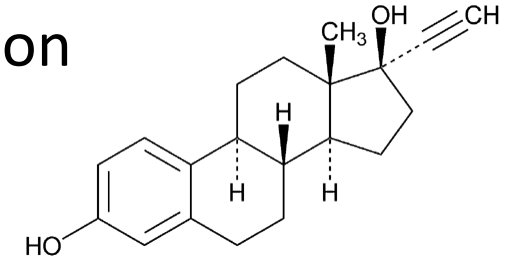


3. Combined contraceptives

Which hormones are used?

3. Combined oral contraceptives

- The most common method of contraception

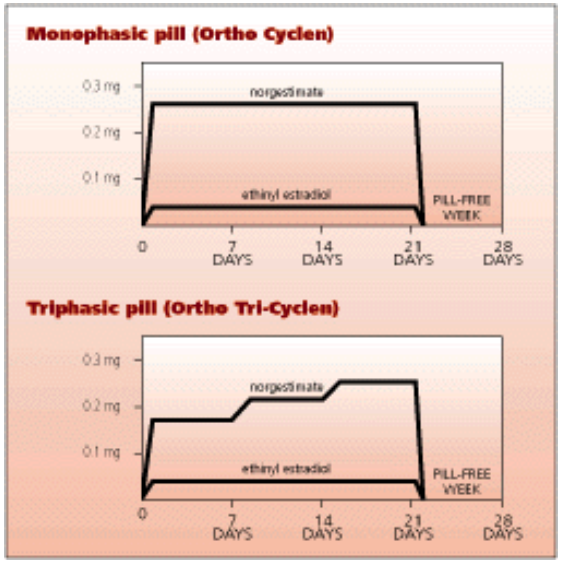


- Always **combinations:**
- ethinyloestradiol (estradiol valerate, 17β-estradiol) + progestin

- Currently, medicines containing **progestins of the third generation**

- Low-dose hormone preparations

- Usually one-phase and three-phase combinations



3. Combined oral contraceptives

What are **dosing regimens** of combined contraception?

Dosing modes:

- packing regimens beginning with Sundays - one tablet a day, starting on **the first Sunday** after the onset of menstruation. If the menstruation begins on Sunday, the first tablet is taken on the same day

- 21-day regimens - one tablet is taken daily for 21 days, starting on the **5th day of the cycle**. After using all 21 tablets, the contraceptive is not used for 7 days, and then new packs are being used

- 28 day regimens - 1 tablet per day is used continuously

3. Combined oral contraceptives

What interactions do you know?

Combined contraceptives - drug interactions

A) Induction of liver enzymes; **ethinylestradiol is a CYP3A4 substrate**
- barbiturates, phenytoin, barbiturates, carbamazepine felbamate, rifampicin, topiramate, primidone, ritonavir

B) Disruption of reabsorption in **enterohepatic circulation**
(ATB broadband)

The first warning about drug interaction can be **bleeding!**

Up to 30% of women taking OCPs exhibit a **deficiency in folic acid 1**and deficiency persists for up to 6 months after discontinuation.

They can lower vitamin **B6 and vitamin C levels**.

Combined contraceptives

What about the **forgotten dose?**

Forgotten dose - follow the PIL!

Combined contraception:

- if you forgot 1 tablet, take it as soon as you remember or 2 tablets the next day
- if forget 2, use 2 for the next 2 days
- if you forget 3 or more, stop taking the tablets
- in all cases, to **insure contraception by alternative methods**

Gestagens:

- if you forgot to take 1 tablet, take it as soon as possible and then another tablet at the time you have chosen
- if two tablets are forgotten, omit them altogether and take up the next dose at the scheduled time
- if 3 tablets are forgotten, discontinue therapy and provide adjuvant contraception for further menstruation.

Specific preparations

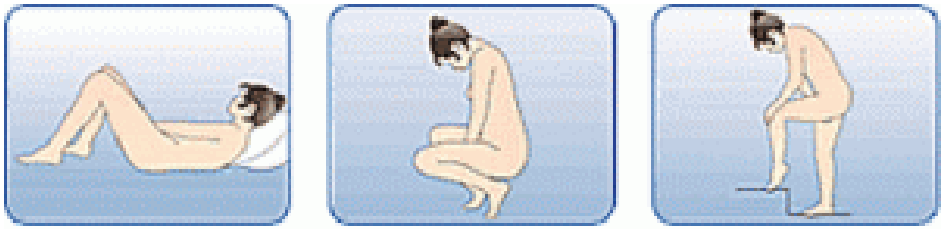
- **Evra patch** (norelgestromin and ethinylestradiol)
- Stable plasma concentrations

- 1 patch **for 7 days** (3 weeks of application)
- Pure, dry, uncovered skin (not breast)
- Never stick to irritated skin
- One anatomical area within 1 cycle
- Never stick to the same place twice
- At exchange day - Replace immediately at any time of day

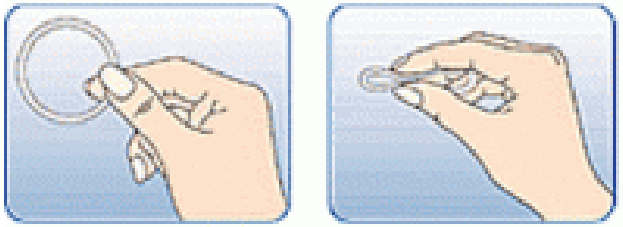
Specific preparations

- **NuvaRing vaginal insert** (Etonogestrel 11.7 mg, Etinylestradiol 2.7 mg in 1 vaginal ring)

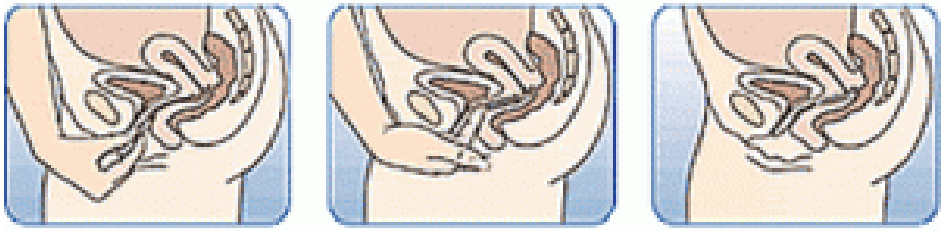
- Keep it in refridgerator
- application **once a month (3 weeks)**
- If the ring is accidentally ejected, it can be rinsed with cold or lukewarm water (not hot) and immediately re-introduced. If it was outside of the vagina for less than 3 hours, contraceptive efficacy is not reduced



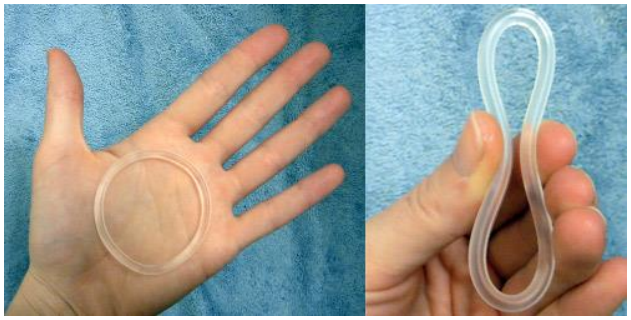
Step 2: Choose a position that is comfortable for you.

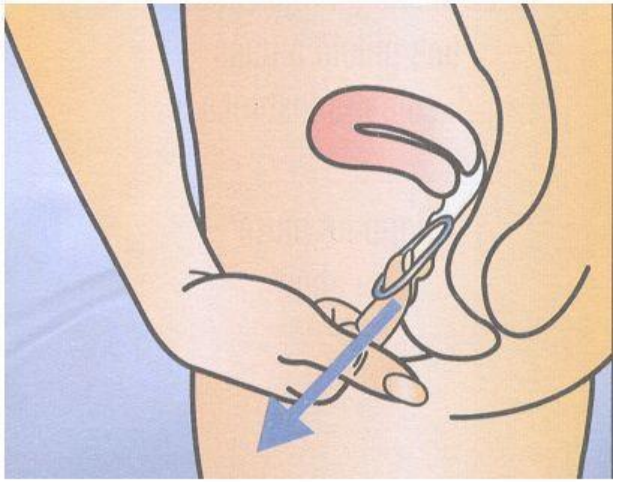


Step 3: Press the opposite sides of NuvaRing® together and gently insert it.



Step 4: NuvaRing® can be positioned anywhere inside the vagina.



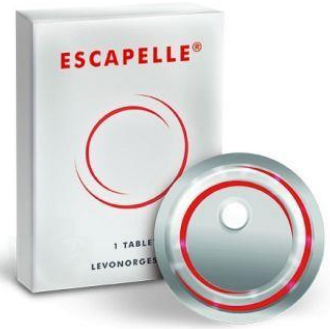


4. Postcoital contraception

- High doses of gestagen
- **Postinor - 2 tablets** (750g levonorgestrel) - 1 tablet and the other after 12 hours. 593,- CZK
- **Escapelle 1tbl** - (1500g levonorgestrel), can be used within 48 hours, 72 hours ?? but the sooner it is used the better. 493, - CZK
- **High doses of conventional contraceptives** such as **Microgynon tbl.** (ethinylestradiol, levonorgestrel) at 4tbl. and within 12 hours another 4tbl.
- Bleeding 3 days after administration, continuation of OCPs is not contraindicated
- Can be used max. once a week, menstrual cycle disruption
- ADR: headache, nausea, pain of abdomen, if vomiting in the first three hours to give another tablet

Postcoital contraception

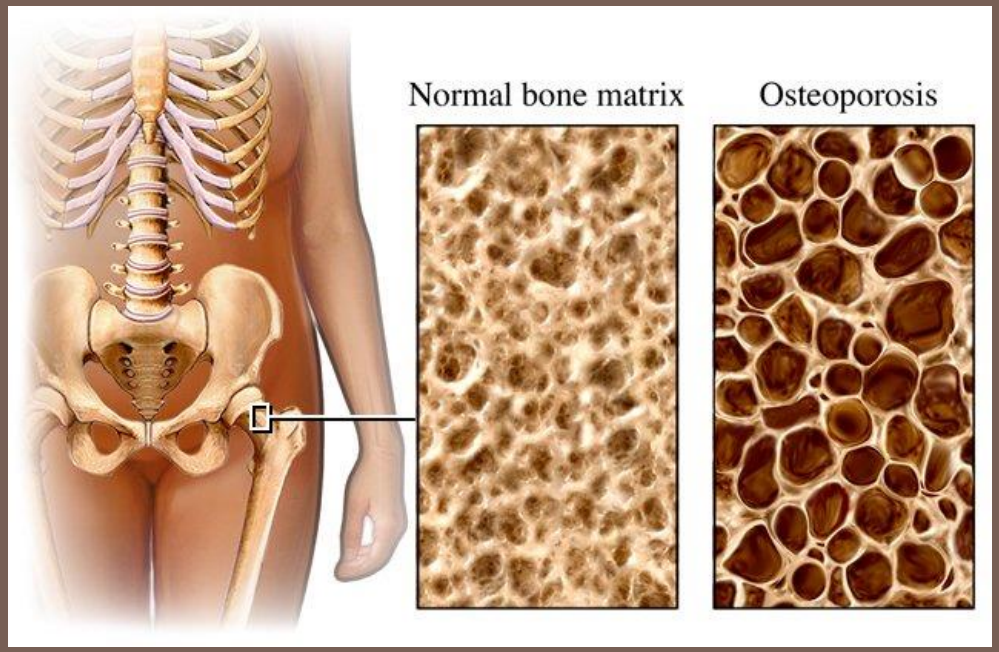
- It is necessary to thoroughly educate the client and carefully evaluate the data obtained
- From age of 16
- Pick up - in person
- The reason for contraception. Why?
- Exclusion of pregnancy
- **KI:** malabsorption sy, liver dysfunction, history of ectopic pregnancy…



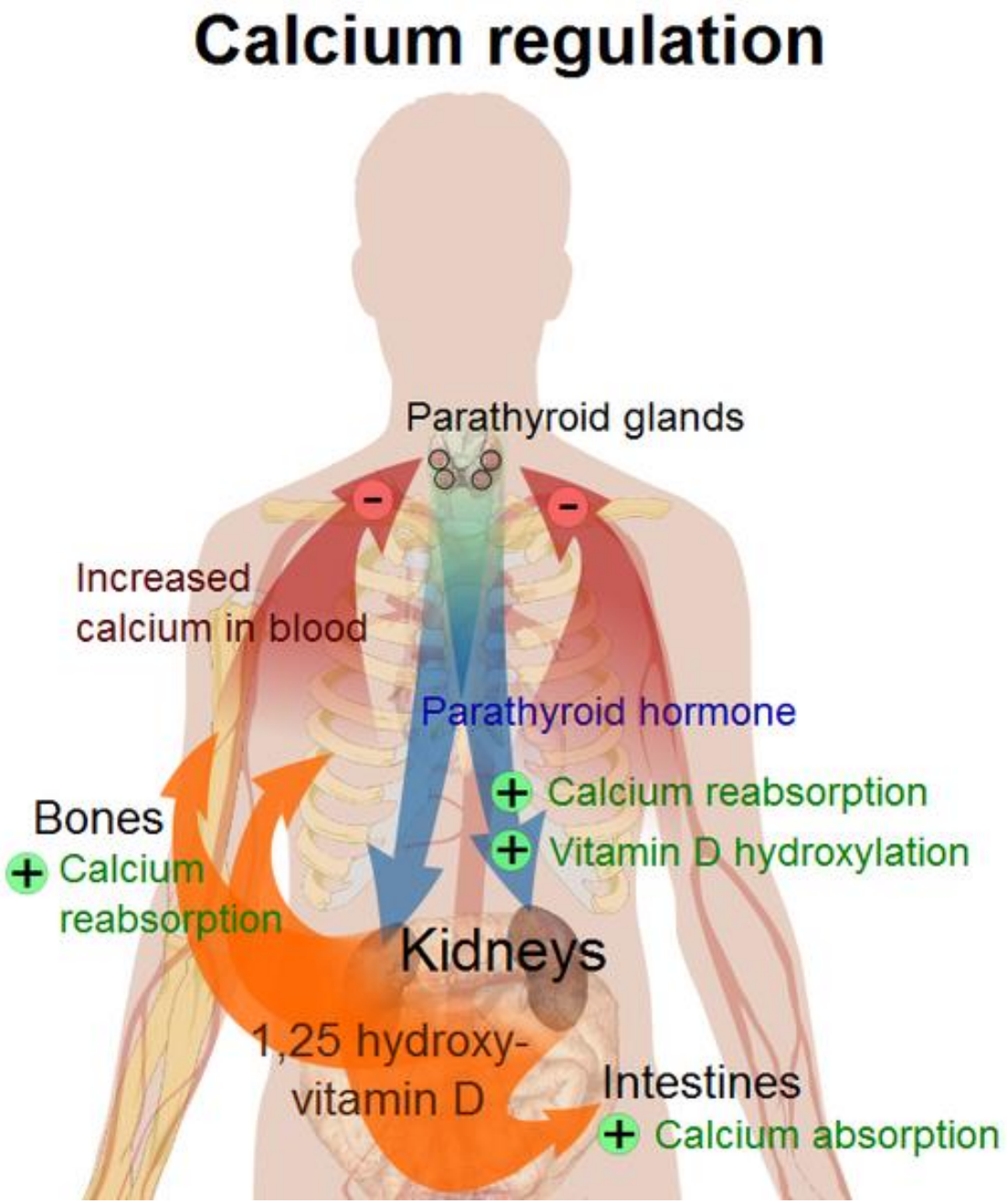
ulipristal-acetate (Ellaone) 660,-Kč

- **effective up to 120 hours (5 days) from sexual intercourse**
- therefore it is not recommended under 18 years
- A significant limitation is also for nursing women - breastfeeding should be interrupted for at least 36 hours
- Not with severe liver damage
- adverse affect for the ability to drive and use machines
- until the beginning of further menstruation with a reliable barrier method (condom
- especially **for cases between 72 and 120 hours** after sexual intercourse, when the two previous products can not be used.

Osteoporosis



Metabolism od calcium



Bone metabolism

- Bone tissue is metabolically very active (spongiosa)
- Continuous **bone remodeling**
    - **osteosorption and formation**
- Both the volume and the strength of the bone depend on the balance of both these processes.

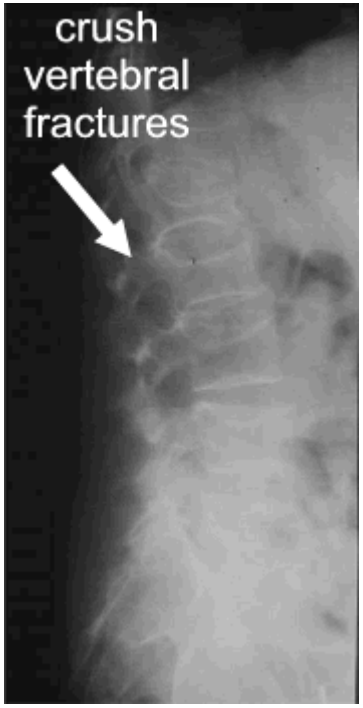
Remodeling is provided by bone cells:

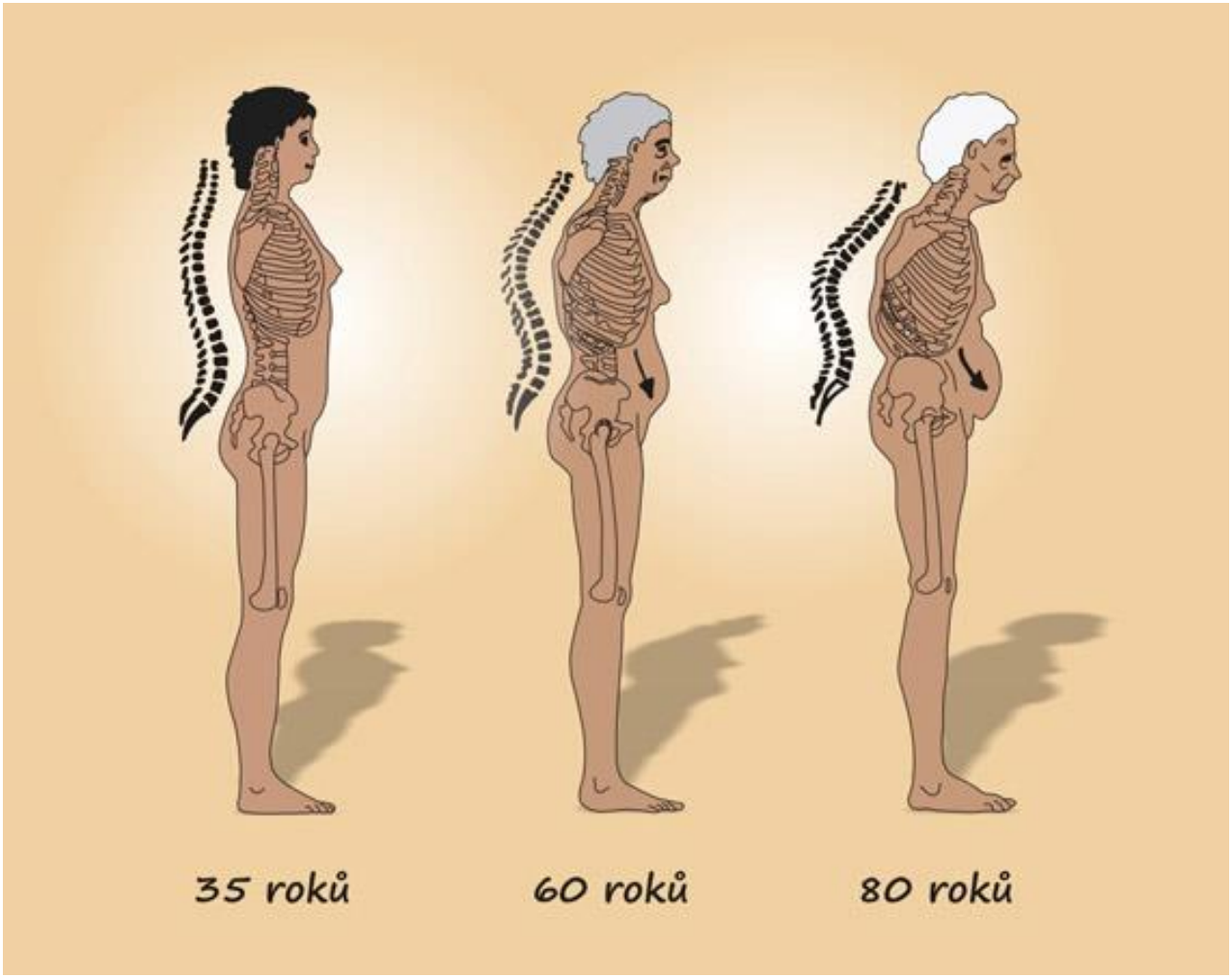
- osteoclasts (modified macrophages, bone resorption)
- osteoblasts (type of fibrocytes, neoplasm of bone tissue)
- osteocytes (resulting from the conversion of osteoblasts) that

Osteoporosis - systemic disease of the skeleton

- **loss of bone mass** while maintaining a normal ratio between mineral and organic bone
- as a result of a **negative balance** of bone mass
- reducing **bone strength**
- **low bone density**
- deterioration of **bone microarchitecture**
- susceptibility to fractures
- loss of organic and inorganic components (both)

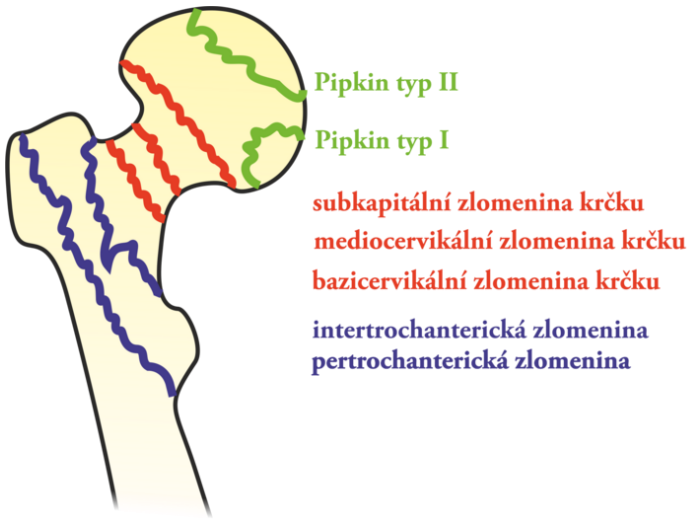
One-sided vertebral dislocation, the thoracic vertebra arches. After the 70th year, the likelihood of compression occurring in the vertebrae of **each second woman**



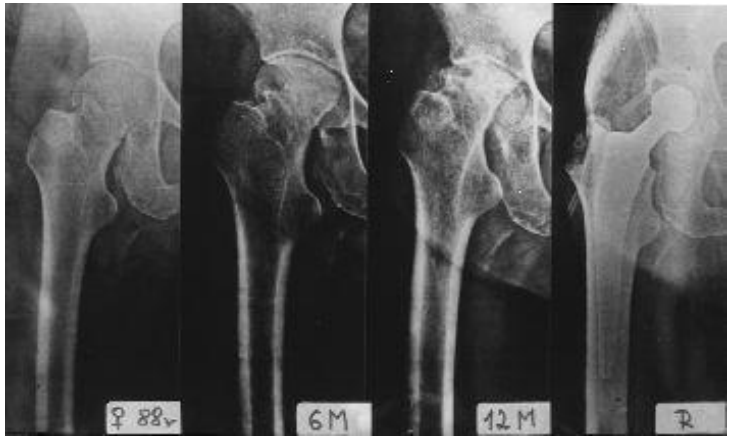


Fracture of the proximal femur

- 20-30% of patients per year die after fracture
- 30-40% is permanently dependent on the care of others



Štěpán J, Havelka S, Kamberská Z. Epidemiologie der Osteoporose in der Tschechischen Republic. J Mineralstoffwechsel 2002;9(3):7-13.



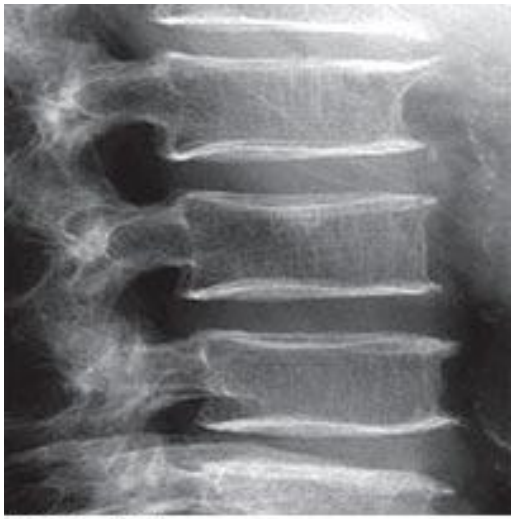
OSTEOPOROSIS RISK FACTORS

- A • Alcohol Use
- C • Corticosteroid Use
- C • Calcium Low
- E • Estrogen Low
- S • Smoking
- S • Sedentary Lifestyle

"Access" (leads to) Osteoporosis

Diagnostics of osteoporosis

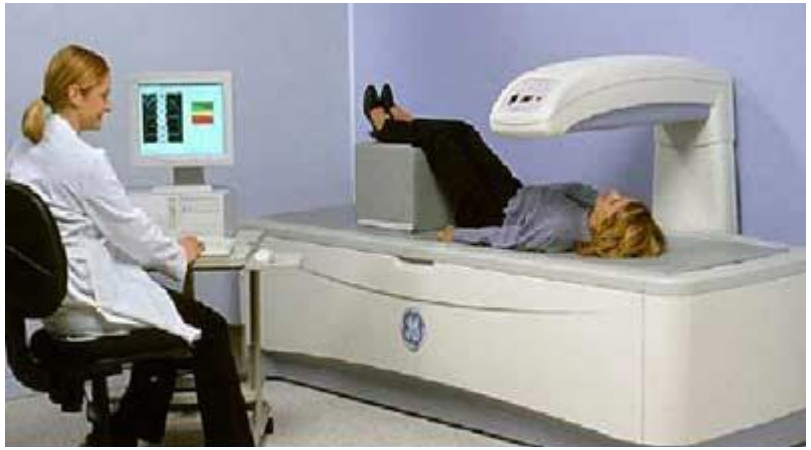
- Anamnesis - risk factors
- Clinical examination
- Laboratory examination
- Bone densitometry
- X-ray examination
  - **thoracic and lumbar spine** in lateral projection a
  - lumbar spine in the back projection for verification
  - the presence of fractures of the **vertebral bodies**
  - bone loss can not be determined
- Examination by rehabilitation worker



RTG páteře.

X-ray Absortiometry (bone densitometry)

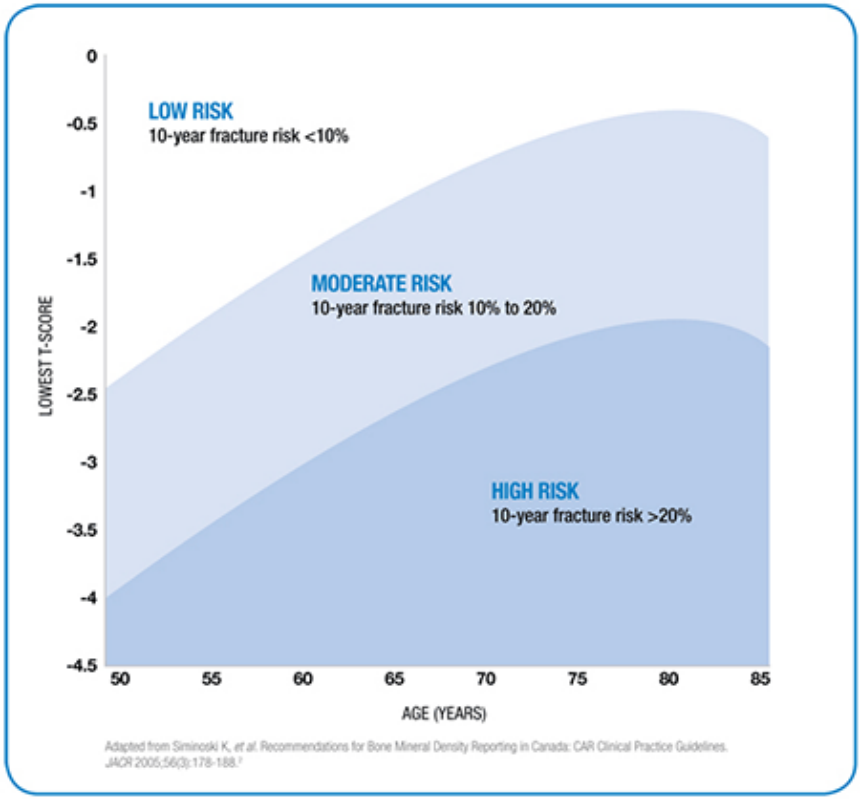
- The standard of diagnostics is
- Dual-Energy X-Ray Absorptiometry (DXA)
- Densitometry output - Bone Mineral Density, BMD
- the most quantitatively predictable osteoporotic fracture predictor
- Measurement of predilection sites of fractures**: femoral neck, lumbar spine**



Bone densitometry

- The result is expressed as the **Planar Bone Density (BMD) in g/cm2** and compared to the healthy population.

T-score
comparison of the measured value versus the mean value of young healthy adults of the same sex (SD) - dg in postmenopausal women



R... L.

Droit COL FEMORAL DENSITE OSSEUSE

Lieu:
90 ans: 24.09.1911
150 cm 48 kg Blanc Féminin
Médecin:

Acquisition: 11.03.2002 (4.7c)
Analyse: 11.03.2002 (4.7c)
Impression: 11.03.2002 (4.7c)
ruffil01.f27

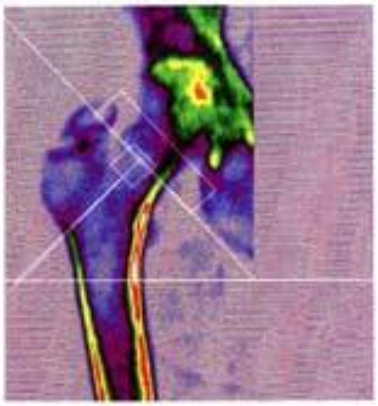
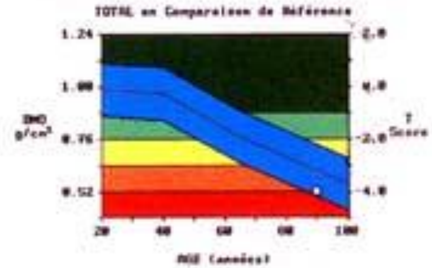
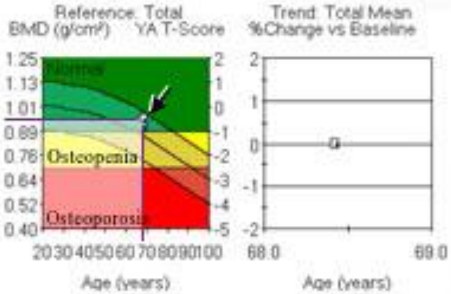


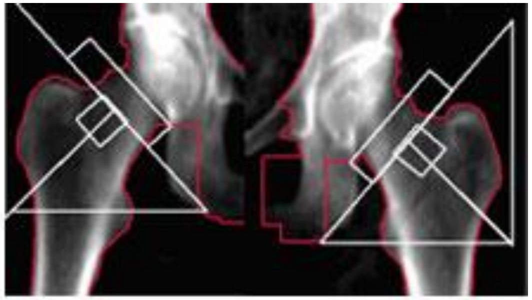
Image Non Diagnostique



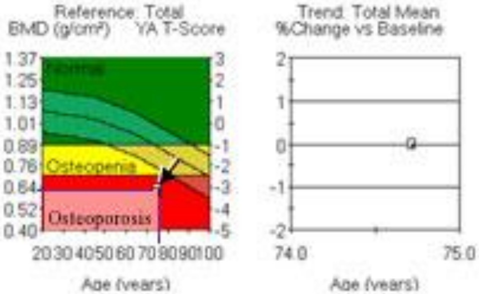
Région	DMO g/cm²	Adulte-Jeune %	Adulte-Jeune T-Score	Age-Egal %	Age-Egal Z-Score
TOTAL	0.523	52	-4.0	85	-0.8

68 year old woman





74 year old woman



Therapy of osteoporosis

Therapy of osteoporosis

- Pain relief
- Nutrition
- **Exercise and physiotherapy**
- Supplementation of calcium and vit. D
- **Medication treatment**
- Orthoses, lumbar belts
- Surgery
- Social support

- Active cooperation of the patient !!!

Prevention of osteoporosis

- maximum **"peak bone mass"**
- treatment of chronic childhood illnesses
- eliminate risk factors and GIT dysfunction
- a varied diet - calcium, vitamin D
- active movement, increase physical activity
- HRT

Pharmacological treatment

Inhibition of bone resorption

- Estrogens
- Bisphosphonates
- (Calcitonin)
- SERM - raloxifene
- Strontium ranelate
- Calcium
- Denosumab

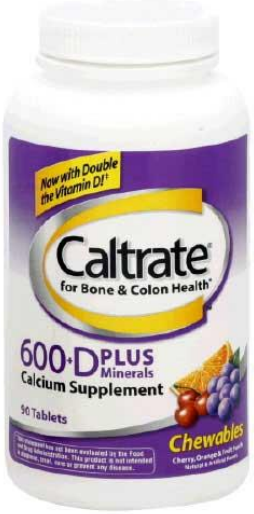
anti-resorptive therapies - bisphosphonates with the amino group in the side chain

Stimulation of bone formation

- Vitamin D
- Anabolics Teriparatid
- Strontium ranelate
- Osteogenon
  - organic elements of bone (ossein) and microcrystalline hydroxyapatite) containing calcium and phosphorus
  - In ossin protein and non-protein substances with a positive effect on the formation of bone tissue.

Calcium - Ca^{2+}


Calcichew D3
60 žvýkacích tablet
Calcium 500 mg
Vitamin D3 200 I.U.


Now with Double the Vitamin D!
Caltrate
for Bone & Colon Health
600+D PLUS Minerals
Calcium Supplement
90 Tablets
Chewables

Nutrition - general recommendations

- Daily 3 servings of low fat milk and dairy products (3 dcl of milk, 1 yoghurt, 50g of cheese)
- Vegetables and fruits rich in calcium

- Vitamin D (fish, liver, cheeses)

- Enough movement
- 0 smoking, 0 alcohol, ↓ coffee
- Restrict phosphates (Coca-Cola Processed Cheese)
- Reduce oxalates (rhubarb, asparagus, spinach, cocoa)

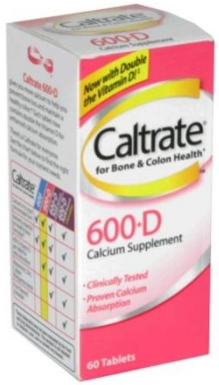
Recommended calcium intake:

- All 19-65 .. 1000 mg
- Men under 65 .. 1500 mg
- Pregnant> 19 years .. 1000mg
- Pregnant <19 years .. 1200mg
- Nursing> 19 years .. 1000mg
- Nursing <19 years .. 1200mg
- Women before and after manopause with HRT .. 1000mg
- Women before and after manopause without HRT .. 1500 mg
- Men and women over 65 with osteoporosis .. 1500 mg
- Men and women over 65 without osteoporosis .. 1000 mg

Apps in the evening, or divide during the day

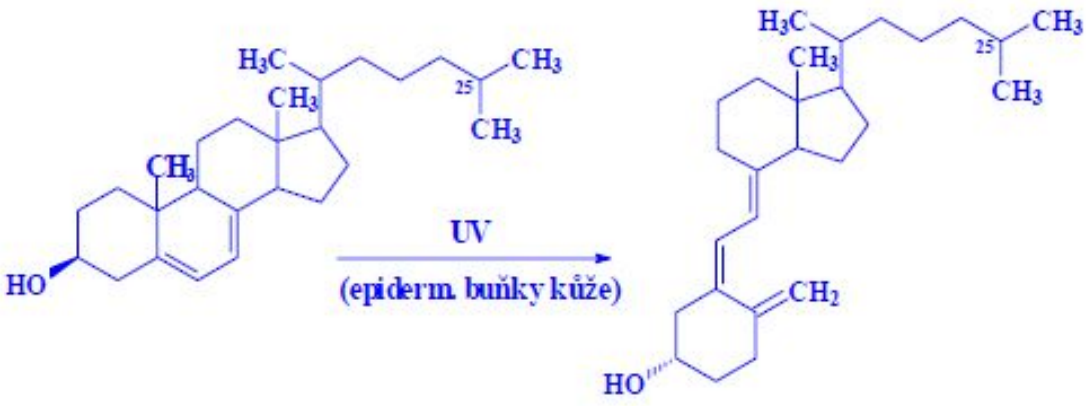
Calcium preparations

- increasing the supply of calcium to mineralization
- cheap, as monotherapy, however, little effective
- daily intake sufficient in food (1 g)
- frequent constipation
- therapeutically 500 mg daily
- *calcium lactate or gluconate*



- calcium salts have no documented effect on improving osteoporosis, but
- Calcium deficiency is worsening, ranging from 70 years in women

Vitamin D (cholekalciferol, ergokalicferol)



7-dehydrocholesterol → cholekalciferol

(provitamin D_3) (vitamin D_3)

ergosterol → ergokalciferol

(provitamin D_2) (vitamin D_2)

Vitamin D - function

- Stimulates osteoblasts - releases calcium from bone cells and mineralizes bone with this calcium
- stimulates calcium absorption in the intestine - increases the production of calcium-binding protein in the intestine, promotes the transfer of calcium from the intestine to the intestinal epithelial cells
- increase in supply of Ca 2+ (mineralization support)
- increases reabsorption of calcium in the kidneys
- Inhibits bone resorption by PTH suppression
- **vitamin D increases calcium and phosphorus absorption in the intestine, the synthesis and production of parathyroid hormone decreases and mineralization of bone increases.**

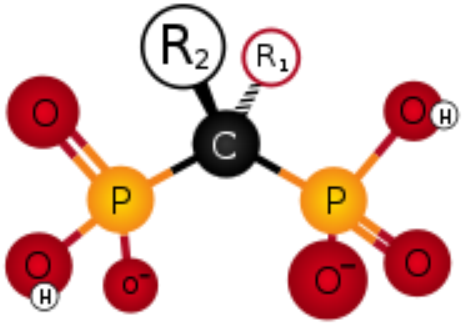
Vitamin D

- 800 IU dose
- ~~Infadin gtt~~
- Vigantol gtt
- Vitamin D Slovakofarma cps
- ~~Calciferol inj.~~
- Combined preparations with calcium

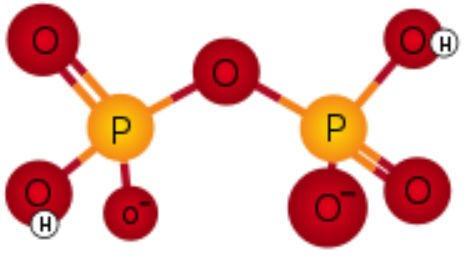
Analogues of vitamin D

- 1 alpha (OH) D3 - alpha-alkacidol (Rocaltrol cps, Alpha D3)
- 19 clone 1.25 (OH) 2 D2 - paricalcitriol (Zemplar)

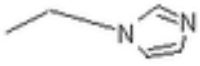
bisfosfonates



Bisphosphonate



Pyrophosphate

Agent	R_1 side chain	R_2 side chain
Etidronate	-OH	$-CH_3$
Clodronate	-Cl	-Cl
Tiludronate	-H	-S-  -Cl
Pamidronate	-OH	$-CH_2-CH_2-NH_2$
Neridronate	-OH	$-(CH_2)_5-NH_2$
Olpadronate	-OH	$-(CH_2)_2N(CH_3)_2$
Alendronate	-OH	$-(CH_2)_3-NH_2$
Ibandronate	-OH	$-CH_2-CH_2N$ (CH_3, $(CH_2)_4-CH_3$)
Risedronate	-OH	
Zoledronate	-OH	

Bisphosphonates

Generation	Chemical structure	Examples	Anti-sorption potential
First	Short alkyl or halogen in the side chain	Etidronate	1
		Clodronate	10
Second	Terminally amino group	Tiludronate	10
		Pamidronate	100
		Alendronate	100-1000
Third	Cyclic side ring	**Risedronate**	1000-10,000
		Ibandronate	1000-10,000
		Zoledronate	10,000+

Bisfosfonates

- They reduce activity, adhesion and the number of osteoclasts
- They induce apoptosis of osteoclasts
- It prevents the attachment of osteoclasts to the surface of the bone
- They reduce bone turnover
- Treatment with bisphosphonates leads to the formation of normal lamellar bone
- Mineral density rise (BMD) and tissue mineralization
- **They do not affect the activity of osteoblasts**

- Effect condition: sufficient supply of calcium and vitamin D

Interaction at absorption level

- Extremely high affinity for binding to divalent cations (Ca2 +, Fe2 +) with subsequent reduction in resorption

optimal adsorption 2 hours before meals

- ↓ Availability at 69% - 1/2 hour before meals
- ↓ Availability at 10% - with food
- ↓ Availability at 34% - 2 hours after a meal
- Irritation of the esophagus and the stomach in daily dosing does not apply when used at longer intervals
- **No other clinically relevant interactions**

In the morning, fasting, drink with plenty of clean water and for 30-60 minutes to eat and not to lie

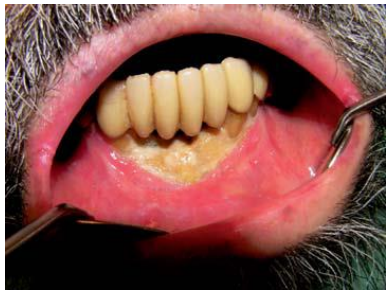
Bisphosphonates – **dispensation minimum**

- standing up, drinking pure water (at least 3 dcl), **30 minutes before a meal**
- Do not crawl, do not chew
- First 30 minutes after a tablet of breakfast until it can lie down again - GER !!!
- **IT:** When taking corticosteroids, absorption of Ca and P from the gut decreases serum Ca levels (possibly hypocalcaemia). The solution is the Ca and D vit.
- Beware of NSAIDs (increase GIT stimulation)

Bisphosphonates

Side effects:

- GIT symptoms - dyspepsia, diarrhea, ... (p.o.)
- musculoskeletal pain, temperature (parenteral)
- bone remodeling disorder - low-energy fracture of long bones
- Osteonecrosis jaws ???



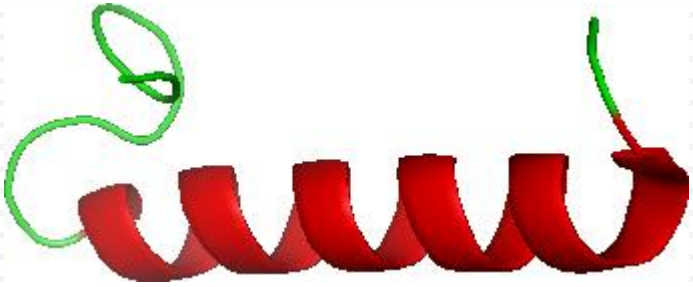
MEDICAL VACANCES FOR 5 YEARS (treatment effect lasts for 1 year)

Indication:

- Osteoporotic fractures
- All forms of osteoporosis including OP induced corticosteroids
- Paget's disease
- Hypercalcaemia associated with bone metastases or multiple myeloma

~~calcitonin~~

Miacalcic spr 200IU, Tonocalcin 200IU spr



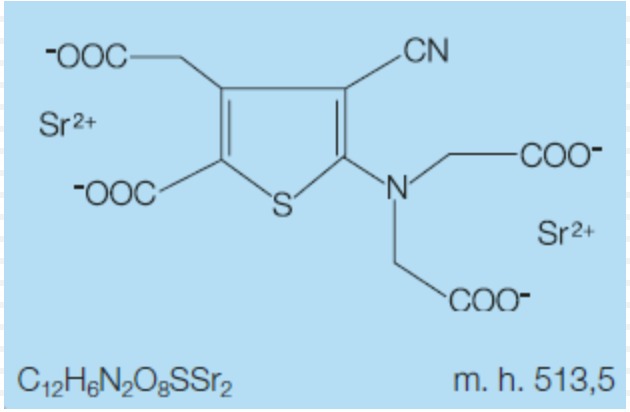
SERM -~~raloxifene~~

- selective estrogen receptor modulators & quot;
- Reduces bone turnover to premenopausal level.
- Increases BMD after 2 years by 2-2.5%
- Higher risk of phlebotrombosis
- Hot flashes. Cramps in the calves.
- Gynecological bleeding
- It reduces the risk of ICHS and ca mammae.
- It lowers LDL cholesterol but does not increase HDL cholesterol

- the first-line drug in high risk first fracture patients?

Stroncium ranelate

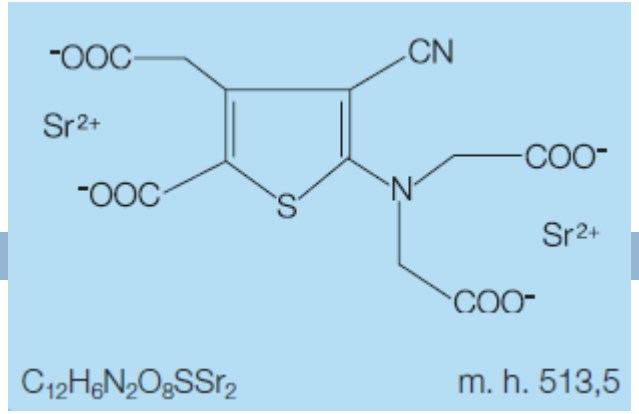
PROTELOS 2 g granular powder for oral suspension (28x2g)



~~Stroncium ranelate~~

- Trace element, fraction in nature 0.01%
- ranelic acid salt, two stable strontium atoms
- Partially incorporated into hydroxyapatite structure - increases the regularity of crystals and bone strength
- Ranel salt ↑ was available (25%) and improved tolerance
- increases the replication of osteoblast precursors, collagen synthesis, and reduces osteoclast differentiation - leads to increased bone formation and decreased bone resorption.
- binding to calcium receptors regulating the secretion of parathormone
- **Increase in new and inhibition of bone resorption 1st. Dual effect medicine !!!**

Stroncium ranelate



- p.o. availability 25%

ADE: rare

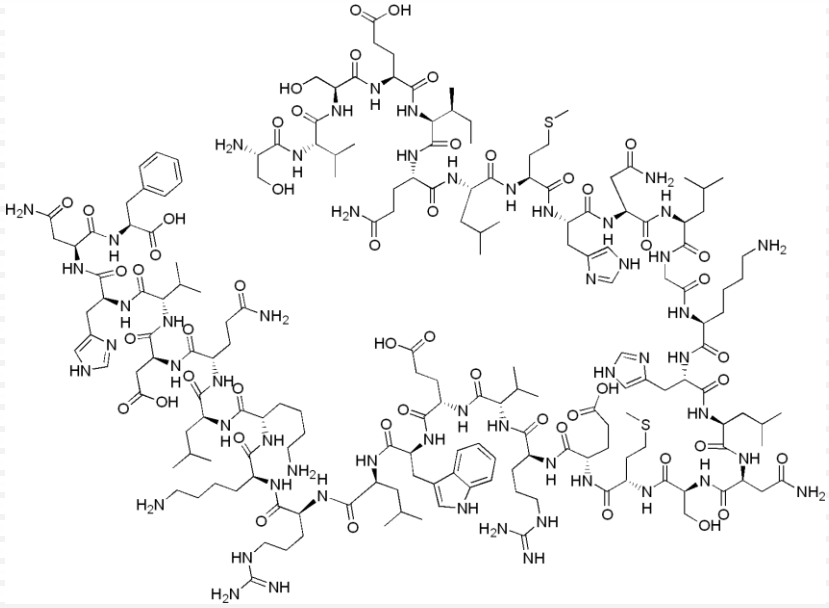
- nausea and diarrhea (treatment discontinuation in 2.2% of patients (1.3% placebo))
- headache, dermatitis, or skin eczema, and elevated liver transaminases

Interaction:

- The bioavailability of strontium ranelate reduces the adsorption antacid, calcium
- complexes with tetracyclines and quinolones
- taking antacids at least two hours after strontium, concomitant use is acceptable.
- **Served 2 g strontium ranelate - 1 times a day, preferably at bedtime at least 2 hours after dinner**

teriparatide

Forsteo inj

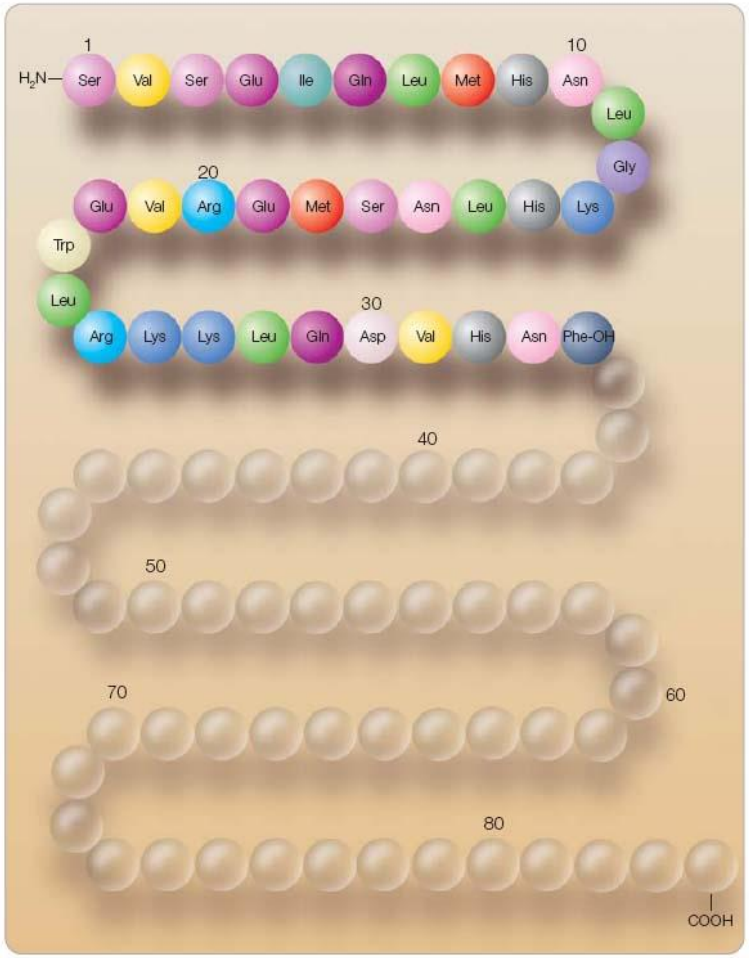


teriparatide

- prevention of progression of postmenopausal or glucocorticoid osteoporosis in case of antiresorptive treatment failure - (expensive, only selected osteocenter, max. 2 years)

- The recombinantly obtained **synthetic parathyroide hormone** amino-terminal 1-34 fragment

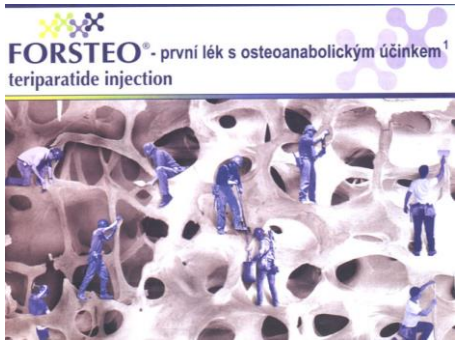
- Maximum effect: in 12 months
- Intermittent administration, **18 months**
- Injection (s.c. 20µg) abdomen



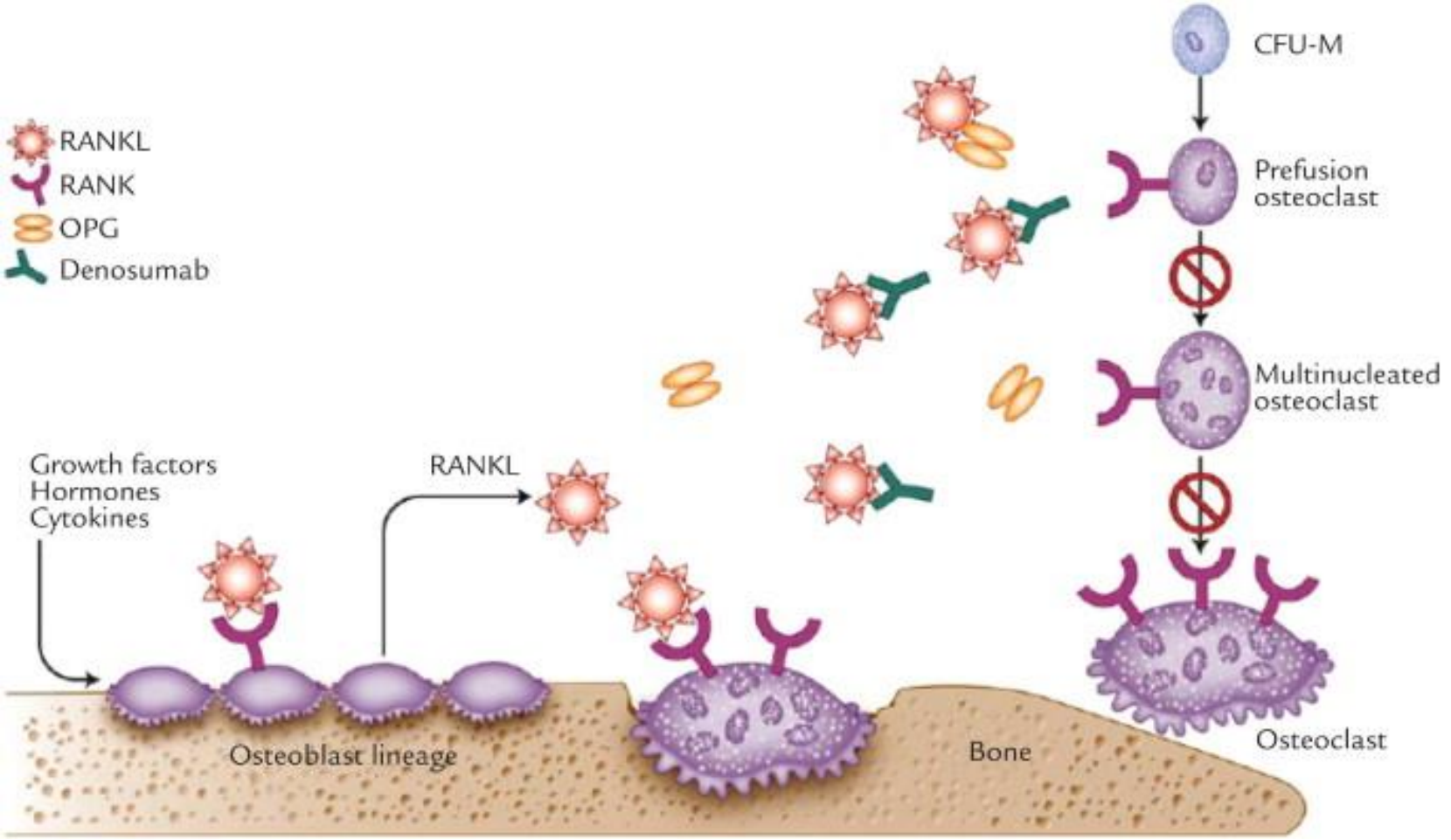
Obr. 1 Teriparatid [rhPTH(1–34)] – sekvence aminokyselin.

Analogue of PTH - teriparatide

- stimulation of osteoblasts → **increase in bone formation**
- suppression of bone resorption effect (against PTH-84 AMK)
- Stimulates bone neoplasm
- It increases the formation of OB
- It reduces apoptosis of OB
- Stimulates bone remodeling
- Improves the number and strength of the trabecu
- Improves the strength of the cortical bone and its geometry
- Effect on VEGF - Vascularization
- ↓ risk of fracture by 65-90%



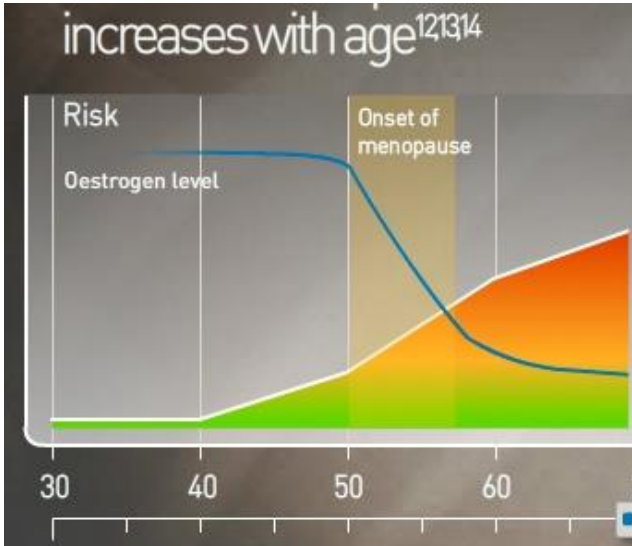
denosumab (Prolia)



denosumab (Prolia)

- Patients prefer subcutaneous injection once every 6 months, instead of once a month (77%)
- Freedom Study (10,000 women)
- Patients with renal impairment do not need to adjust the dose
- Elderly patients do not need to adjust the dose.
- Good tolerance, low IT potential
- Studies have shown a reduction in fracture incidence compared to alendronate

- Postmenopausal women have decreased levels
- estrogen - increased expression of RANK ligand -
- higher activity of osteoclasts



denosumab

- Denosumab - a new anti-resorptive drug that affects the RANK ligand signal pathway and bone biology
- Positive influence on cortical bone
- High affinity for only RANKL of bone cells without neutralizing antibodies
- Denosumab will not accumulate in the skeleto
- Denosumab is not excreted by the kidneys
- Fast reversibility of bone remodeling after disc treatment
- **Single monoclonal antibody according Rp.**