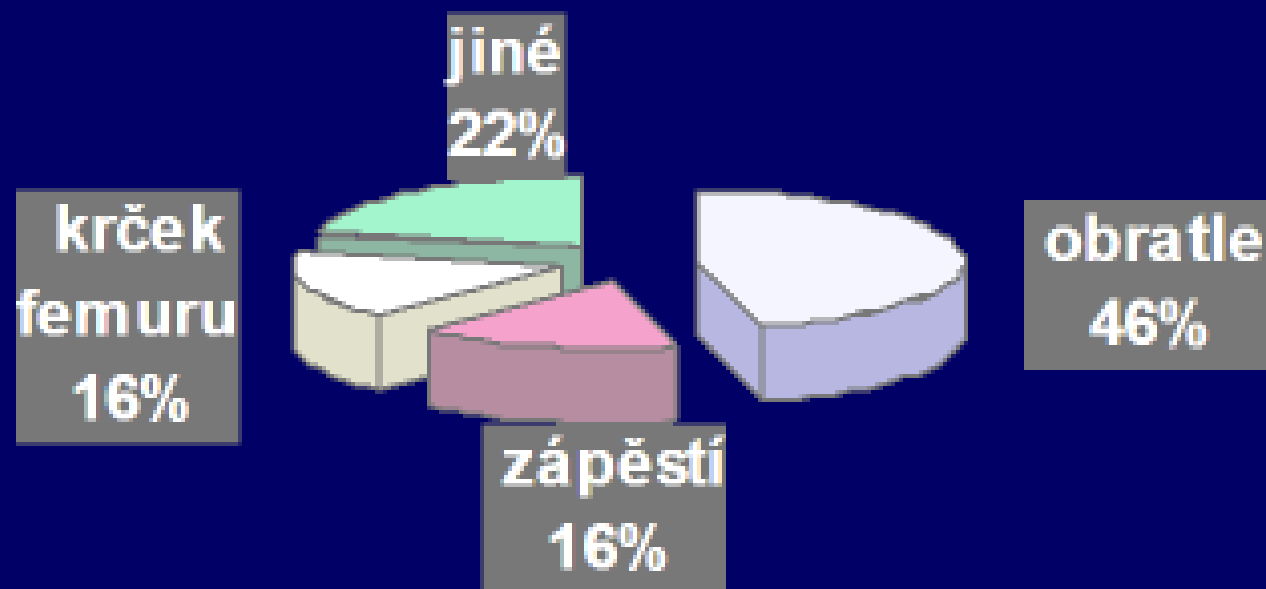


DEFINITION

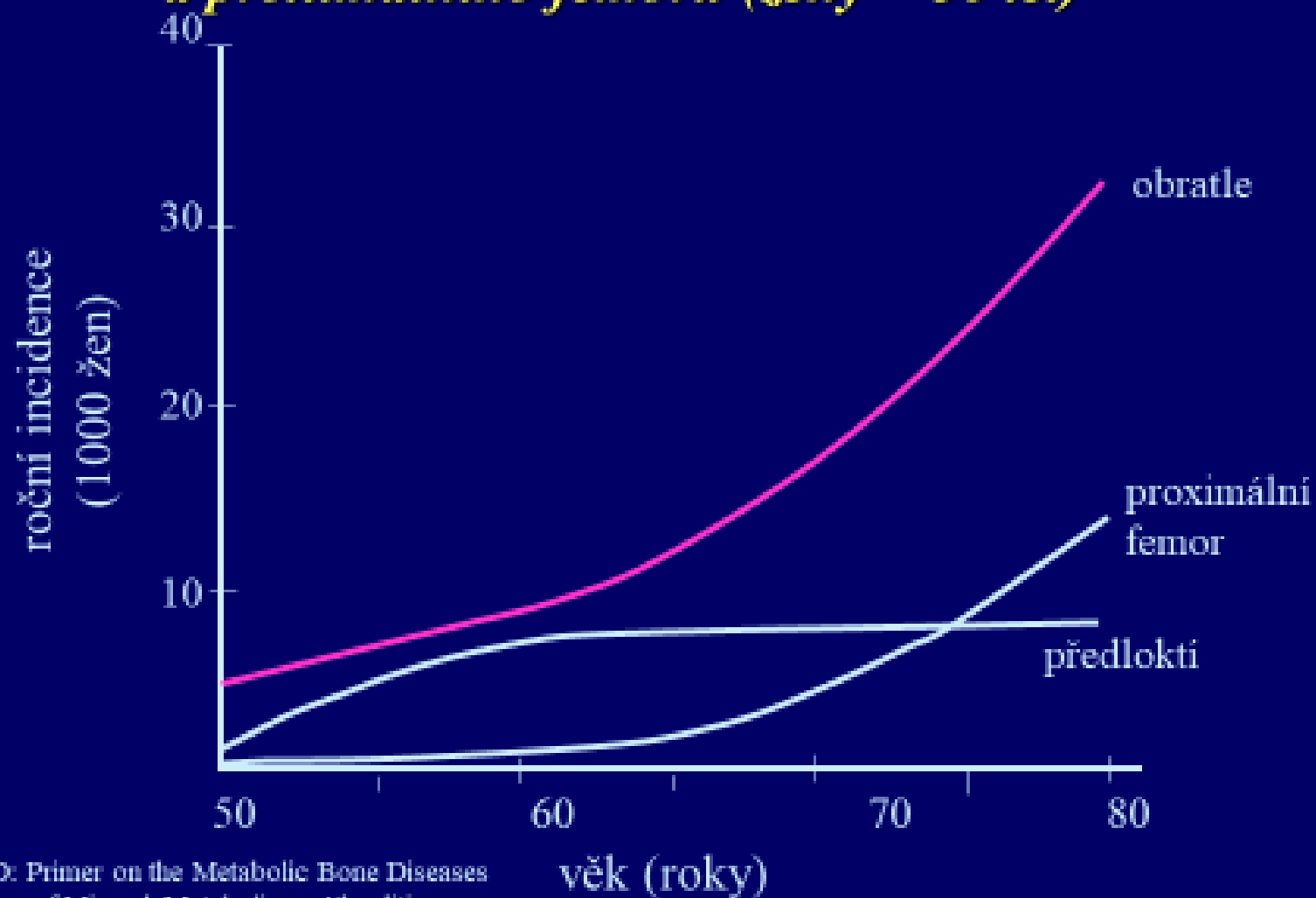
- *Osteoporosis is a systemic skeletal disease characterized –*
- *1. low bone density*
- *2. a micro- architecture deterioration of bone tissue*
- *3. that enhances bone fragility*
- *4. increases the risk of fracture*



Zlomeniny vznikající v důsledku osteoporózy



Incidence zlomenin obratlů, distálního předloktí a proximálního femoru (ženy > 50 let)

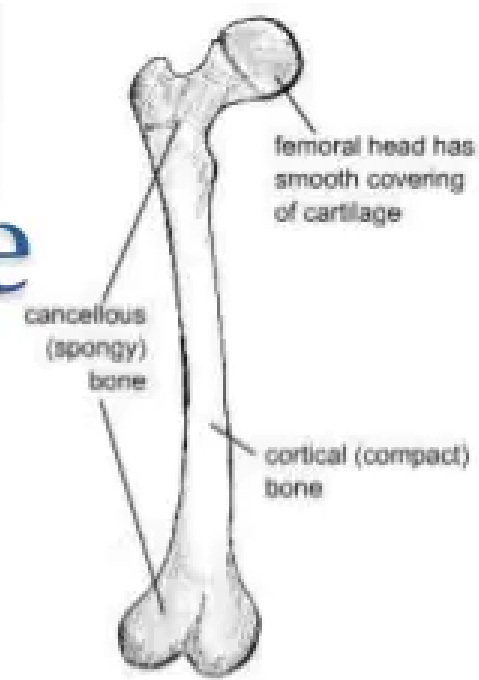




Bone Structure

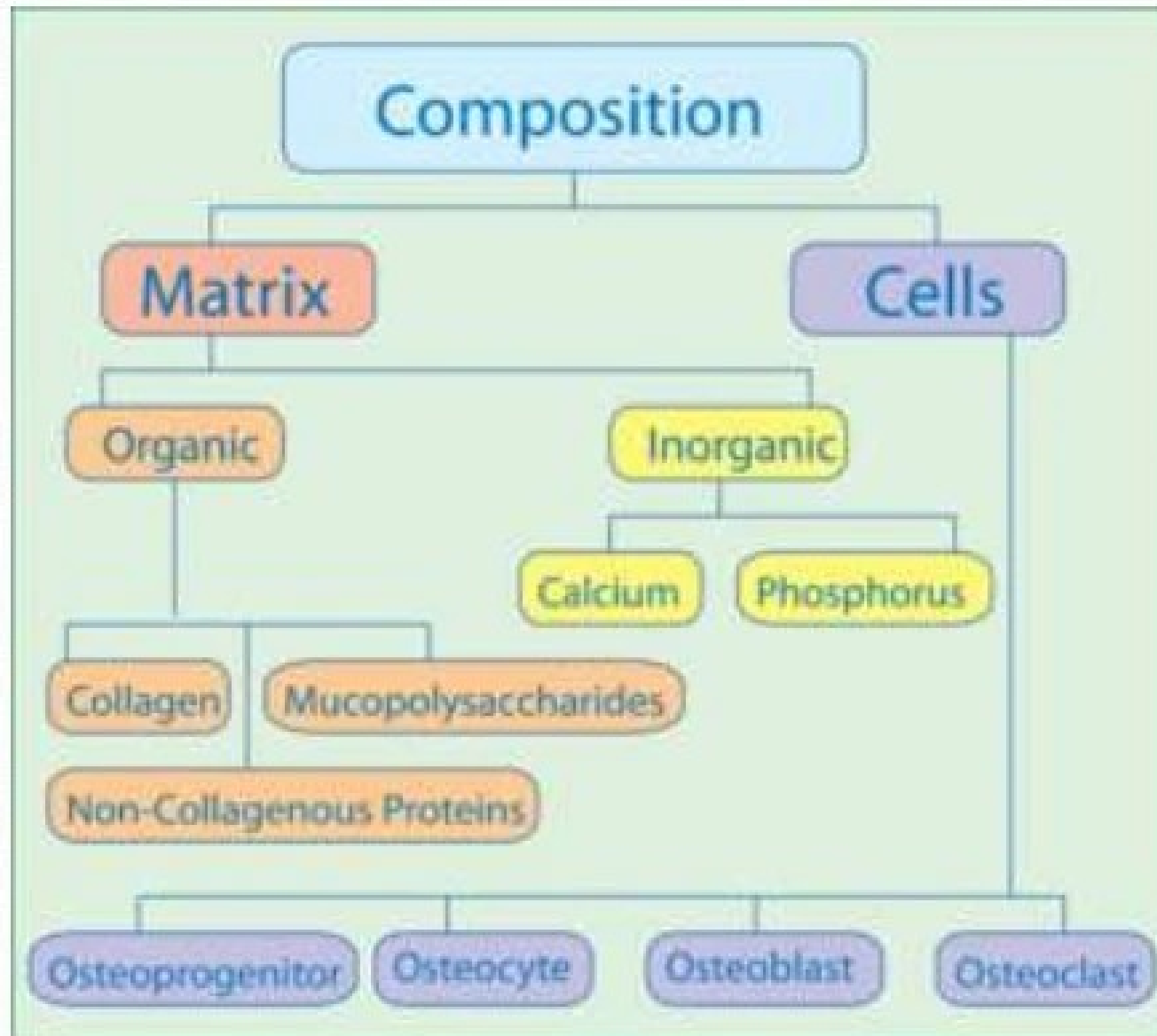
Types of bone:

- **Cortical bone** – 80% total bone mass.
- **Cancellous(trabecular) bone** – 20% total bone mass.



- **Cancellous bone** is formed by an interconnected structure of latticework. It is porous and is often referred to as the spongy inner structure of the bone. Because it is more metabolically active and, has a larger surface area, it is more susceptible to bone loss and fracture.
- **Cortical bone** is the more dense type of bone that surrounds the cancellous bone to form the outer, more durable layer bearing the majority of the body's Weight.

CONSTITUENTS OF BONE



1. Peak bone mass & Osteoporosis

- Peak bone mass is the maximum mass of bone achieved by an individual at skeletal maturity, typically between ages 25 and 35
- **After peak bone mass is attained**, both men and women lose bone mass over the remainder of their **lifetimes**
- Because of the subsequent bone loss, peak bone mass is an important factor in the development of osteoporosis

Determinants Of Peak Bone Mass

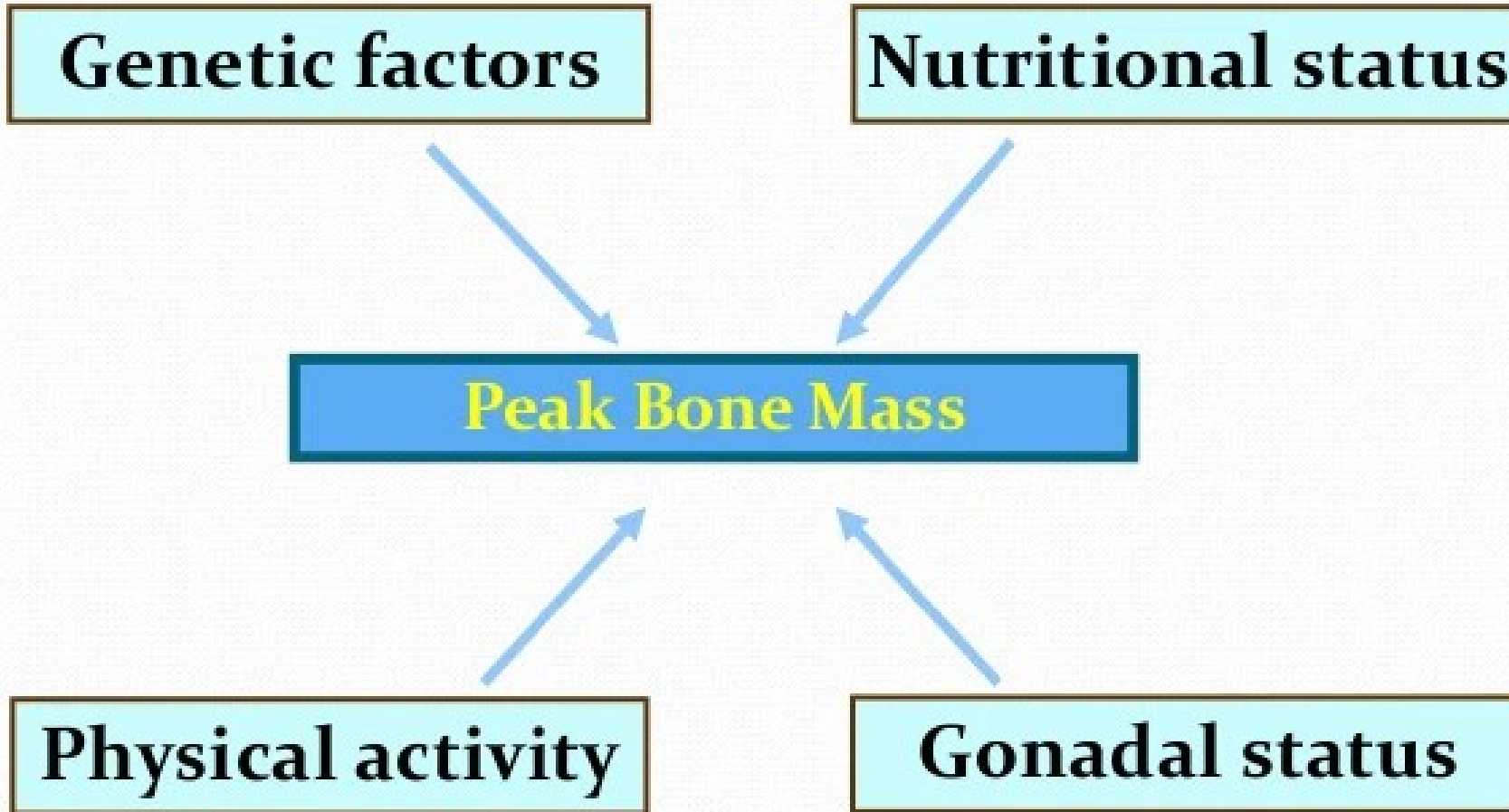
Genetic factors

Nutritional status

Peak Bone Mass

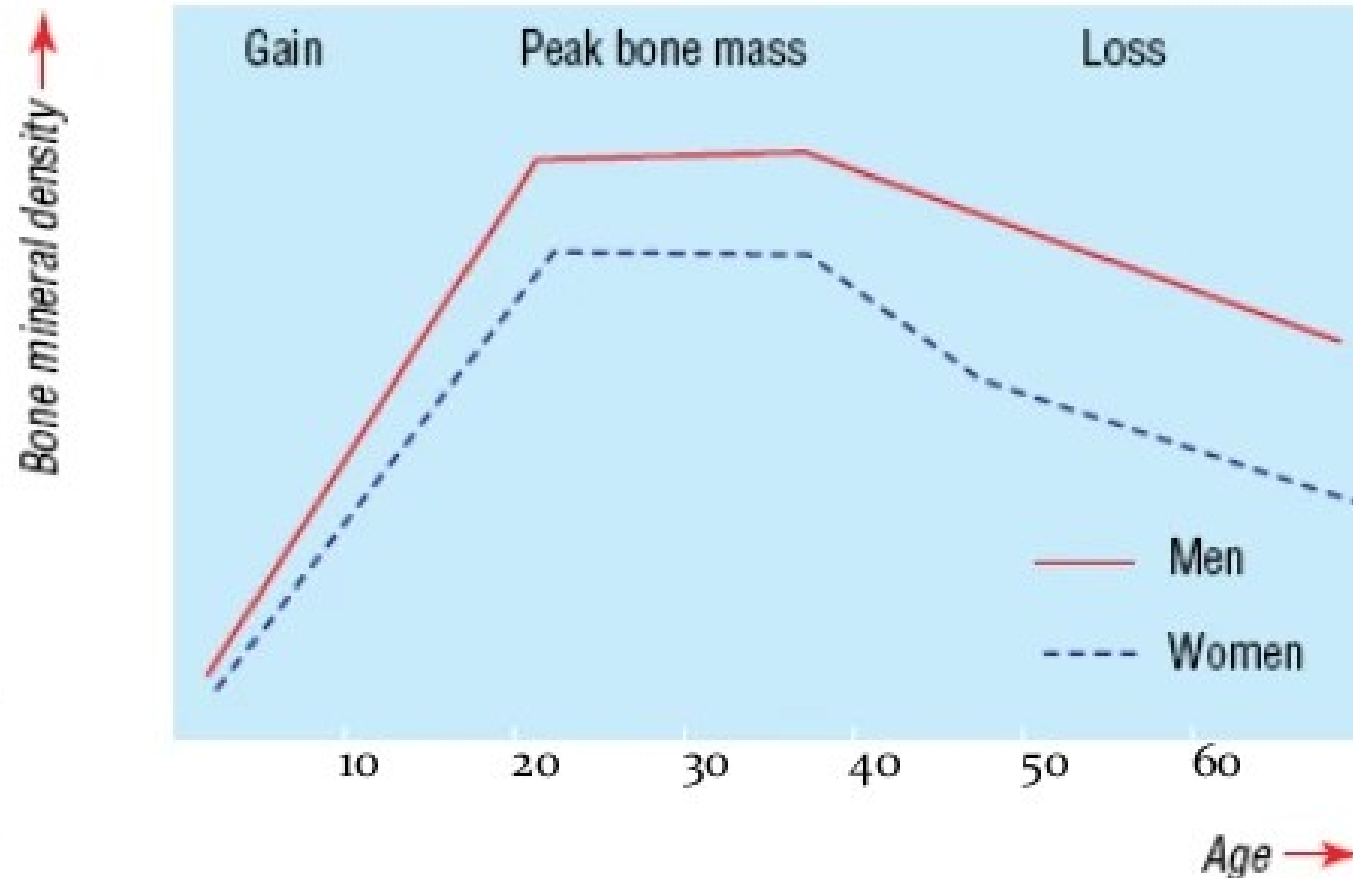
Physical activity

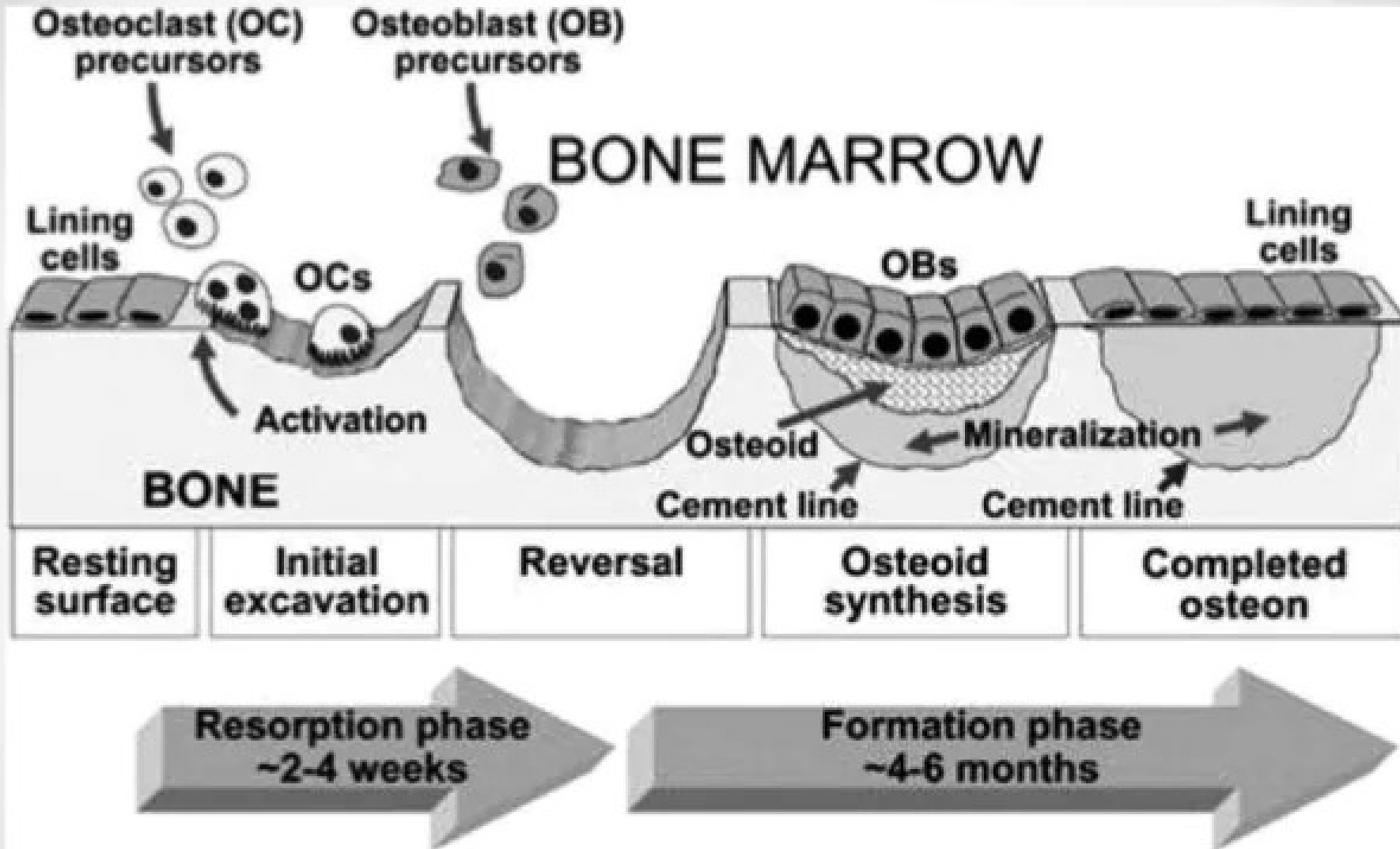
Gonadal status



Peak Bone Mass in Women

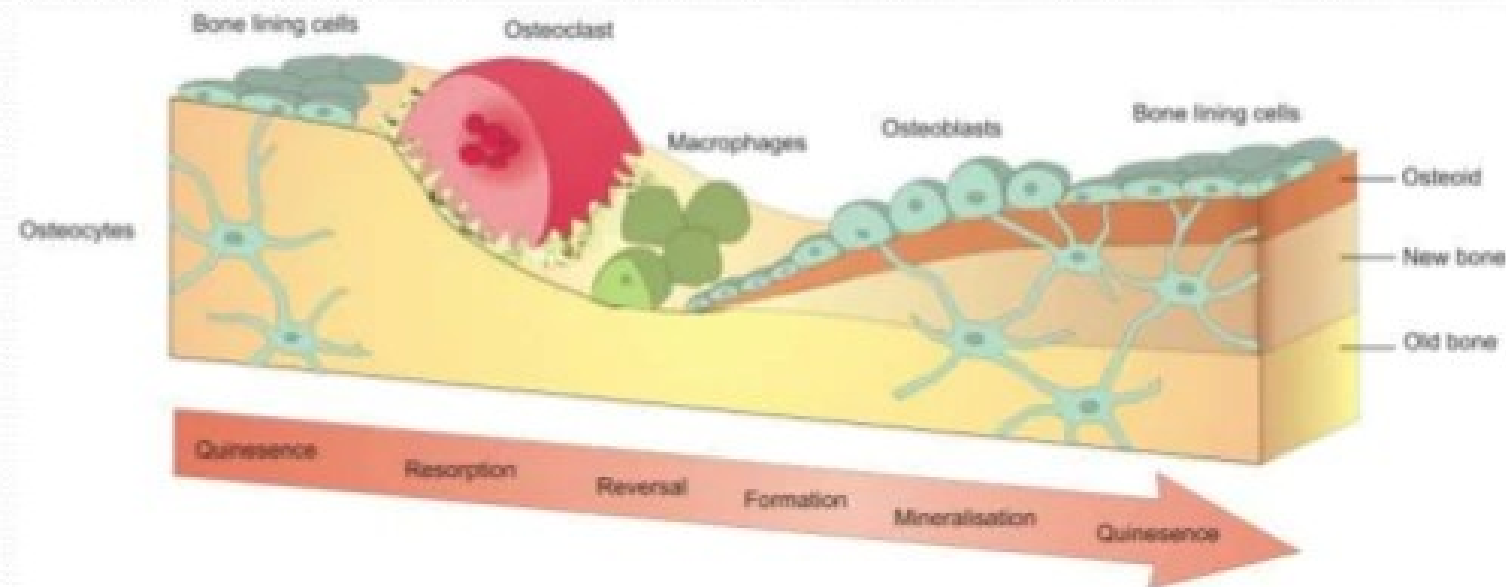
- Women achieve lesser peak bone mass than men





BONE MODELLING AND REMODELLING

- MODELLING- during growth, skeleton increases in size by apposition of new bone tissue on outer surface of cortex.
- REMODELLING- It is a cellular process of bone activity by which both cortical and cancellous bone are maintained.

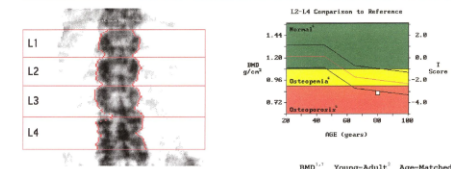


Osteoporosis by WHO

- BMD 2.5 SD or more below the mean for young healthy adult of same gender (**T-score at or below -2.5**).

BMD Interpretation

- Results are generally scored by two measures,
 - ❑ **T-score**
 - ❑ **Z-score.**
- *T-Score* is the BMD at the site when compared to the young normal reference mean.
- *Z-score* is the comparison to the age-matched normal and is usually used in cases of severe osteoporosis.
- Negative scores indicate lower bone density, and positive scores indicate higher.
- Normal : -1.0 or higher
- Osteopenia : -1.0 and -2.5
- Osteoporosis : -2.5 or lower



Range not for diagnosis
 0.786-1.516 (FPO) 1.241-1.486
 73555-41907 275.66-295.21 145.88
 8148 = 29.411.323)

1 - See appendix on precision and accuracy.
 2 - Statistically 95% of repeat scans will fall within 1 SD. (SD: 0.01 g/cm³)
 3 - English 40 Spine Reference Population, Young Adult Age 20-40. See Appendixes.
 4 - Matched for Age, Weight (25-100kg), Ethnic.
 5 - BMD not derived for white women that: < -1.0 SD = normal;
 -1.0 to -2.5 SD = osteopenia; < -2.5 SD = osteoporosis.
 7 - Standardized BMD for L2-L4 is 782 ap/cm². See J Bone Miner Res 1994; 9:1503-1514

Comments:

Definition	Bone Mineral Density Measurement	T-Score
Normal	BMD within 1 SD of the mean bone density for young adult women	T-score ≥ -1
Low bone mass (osteopenia)	BMD 1–2.5 SD below the mean for young adult women	T-score between -1 and -2.5
Osteoporosis	BMD ≥ 2.5 SD below the normal mean for young-adult women	T-score ≤ -2.5
Severe or “established” osteoporosis	BMD ≥ 2.5 SD below the normal mean for young-adult women in a patient who has already experienced ≥ 1 fracture	T-score ≤ -2.5 (with fragility fracture[s])

Normal bone vs. Osteoporotic bone

- The normal bone shows a pattern of strong interconnected plates of bone.
- Much of this bone is lost in Osteoporosis and the remaining bone has a weaker rod-like structure & some of the rods are completely disconnected.
- These bits of disconnected bone may be measured as bone mass but contribute nothing to bone strength.





RANK – RANKL RECEPTOR PATHWAY FOR BONE REMODELLING

- **RANK L-** the cytokine responsible for communication between osteoblasts and other marrow cells and osteoclasts. (receptor activated nuclear factor kappa ligand)
- Secreted by osteoblasts and certain cells of immune system.
- RANK- receptor present on osteoclast.
- Activation of RANK by RANKL is final common pathway for osteoclast differentiation and functioning.
- Osteoprotegerin is humoral decoy for RANK secreted by osteoblasts.

Post menopausal osteoporosis (Type 1)

- Characteristically affects women, between 10 and 20 years following menopause.
- Sex ratio 5:2
- PTH and Ca metabolism is decreased.
- Characterized by high bone turnover and rapid loss of trabecular bone.
- Suffer acutely painful crushing fractures of vertebrae and colle's fracture of distal radius

Senile osteoporosis (Type 2)

- Affects men and women aged Over 70 years.
- Sex ratio 2:1
- Due to chronic effect of bone loss since peak bone mass attained in the 4th decade with a superimposed senile lowering of the rate of bone turnover.
- Affects both cortical and trabecular bone.
- PTH is increased - Reduced Ca absorption and 25OHVit D synthesis
- Decreased Insulin like growth factor concentration characterized by multiple wedge fractures of the vertebrae (often pain free) and fractures of the femoral neck and intertrochanteric femoral fractures

Secondary Osteoporosis

Pharmacotherapy:

- Glucocorticoids
- Thyroid over replacement
- Anticonvulsants (phenytoin, phenobarbital)
- Lithium, aluminium
- Heparin (long-term)
- Drugs producing hypogonadism (aromatase inhibitors, antimetabolite chemotherapy, medroxyprogesterone, gonadotropin-releasing hormone agonists)

Endocrine Disorders:

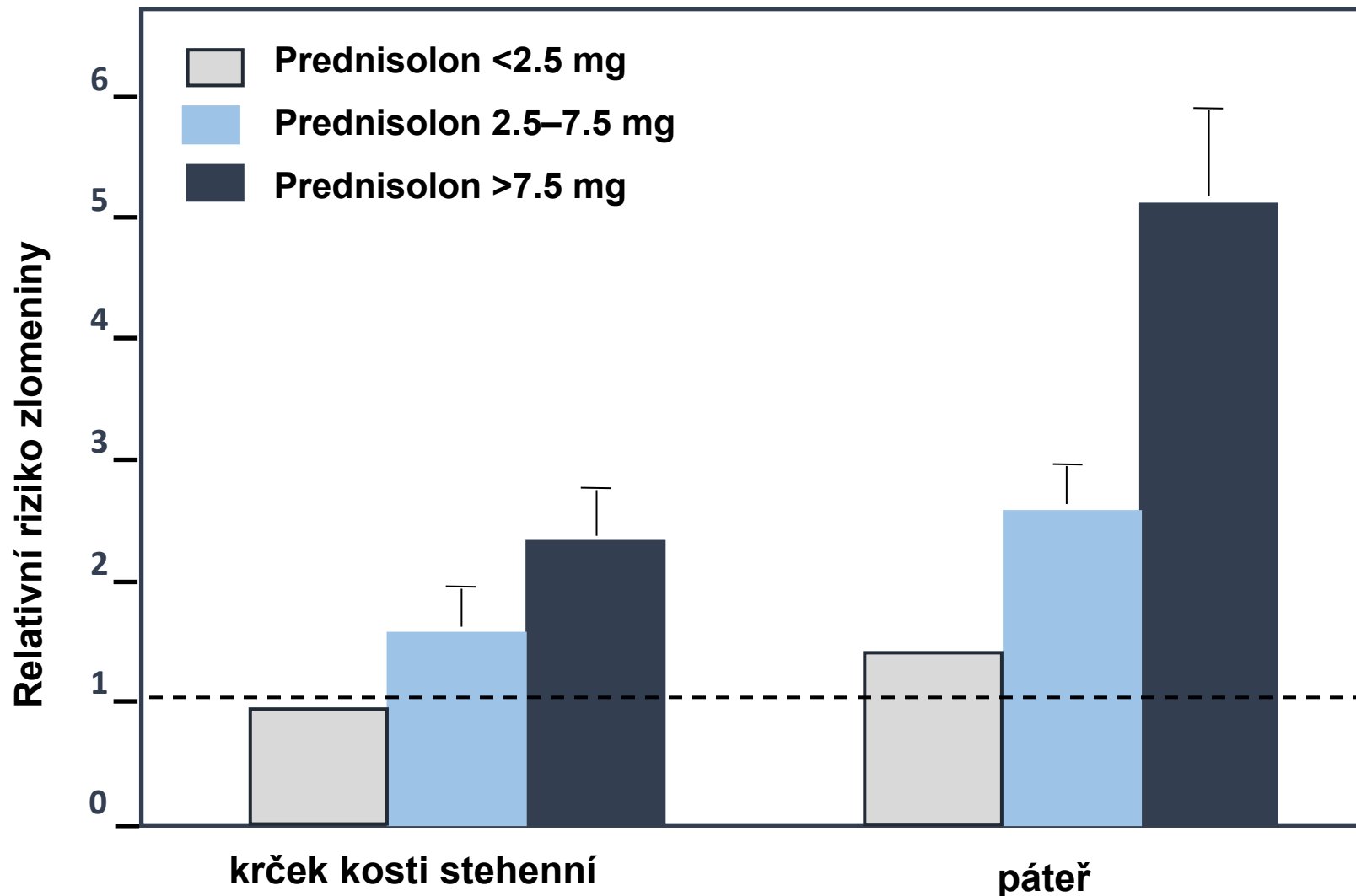
- Cushing syndrome
- Hyperparathyroidism
- Hypogonadism
- Hyperthyroidism

SECONDARY OSTEOPOROSIS

Secondary causes

Endocrine or metabolic causes	Collagen/genetic disorders	Medications	Nutritional	Malignancy / Hematologic disorders	Miscellaneous medical conditions
Acromegaly	Ehlers-Danlos syndrome	Proton pump inhibitors	Alcoholism (> 2 drinks per day)	Multiple myeloma	Chronic liver disease
Athletic amenorrhea	Glycogen storage diseases	Excess thyroid hormone	Calcium deficiency	Leukemia	Chronic renal failure
Diabetes mellitus	Homocystinuria	Systemic glucocorticoid therapy ≥ 3 months	Eating disorders	Lymphoma	Chronic obstructive lung disease
Hemochromatosis	Hypophosphatasia	GnRH agonists	Gastric bypass surgery	Ectopic ACTH syndrome	Rheumatoid arthritis
Hyperadrenocorticism	Marfan syndrome	Heparin (prolonged use)	High caffeine intake	Sickle cell disease	Spinal cord injury
Hyperparathyroidism	Osteogenesis imperfecta	Serotonin reuptake inhibitors	Malabsorption syndromes	Thalassemia	Systemic lupus erythematosus
Hyperprolactinemia	Cystic fibrosis	Phenobarbital	Vitamin D deficiency	Hemophilia	Tobacco use
Hyperthyroidism	Gaucher's disease*	Aromatase inhibitors	Inflammatory bowel disease	Systemic mastocytosis	Organ transplant
Anorexia nervosa and bulimia		Phenytoin	Excess vitamin A		Multiple sclerosis

Riziko zlomenin u pacientů užívajících glukokortikoidy v závislosti na dávce



Bone Turnover Markers

Measures of osteoblast function:

- **Alkaline phosphatase (AP):** The bone alkaline phosphatase is specific for bone and reflects cellular activity of osteoblasts.
- **Osteocalcin (OC):** a hydroxyapatite binding protein synthesized by osteoblasts

Measures of osteoclast function:

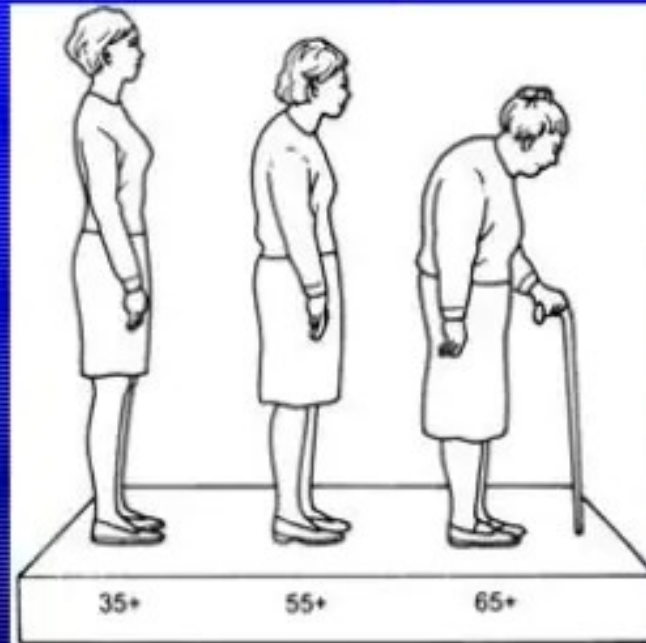
- **Hydroxyproline (OHP):** This reflects breakdown of collagen in bone, cartilage & skin.
- **Collagen crosslinks:** These reflect bone resorption. They tend to be specific markers of bone resorption.

These include the following:

- 1) **N—telopeptide (NTX)** measured in the urine and in serum by an immunoassay termed Osteomark
- 2) **C-telopeptide (CTX)** measured in Serum by an immunoassay termed Crosslaps
- 3) **Deoxypyridinoline (DPD)**

SYMPTOMS

- Back pain, which can be severe if fractured or collapsed vertebra
- Loss of height over time, with an accompanying stooped posture
- Fracture of the vertebrae, wrists, hips or other bones



Risk Factors for Fracture

(Major) with relative risk >2	(Minor) with relative risk 1-2
Age >70	Estrogen deficiency
Menopause <45	Calcium intake <500mg/day
Hypogonadism	Primary hyperparathyroidism
Fragility fracture	Rheumatoid arthritis
Hip fracture h/o in parents	Hypercalciuria
Glucocorticoids	Anticonvulsants
High bone turnover	Diabetes mellitus
Anorexia nervosa	Smoking
<18 BMI	Alcohol
Immobilisation/sedentary life	
Chr. Renal failure	
Transplantation	
Chronic Inflammatory diseases	

Consequence of Fracture

- After the first hip fracture, 30% of patients will fracture the second hip.
- Nearly 20% of the women who develop a new vertebral fracture will fracture again within a year.
- 5 year survival rate following a vertebral fracture is equally worse as a Hip fracture.
- It is clear that bone loss cannot be completely reversed but fracture risk can be decreased by intervention.
- One year mortality following a hip fracture in men is twice that of female

Pharmacological Management

The four major goals in the treatment of osteoporosis are:

- ✓ To prevent fracture,
- ✓ To stabilize bone mass or achieve increased bone mass,
- ✓ To relieve symptoms of fractures and skeletal deformity,
- ✓ To maximize physical function

Léky užívané v léčbě osteoporózy

- HRT
- SERM/Raloxifen
- kalcitonin
- Bisfosfonáty
 - Alendronát
 - Risedronát
 - zoledronát
 - Ibandronát
- Vápník
- Vitamin D

- Parathyroid hormon (PTH)
 - - teriparatid (1-34)
 - - parathormon (1-84)

• Strontium ranelát

* denosumab

PHARMACOLOGICAL PREVENTION OF OSTEOPOROSIS

- Men age 50–70 should consume 1000 mg/day of calcium.
- Women age 51 and older and men age 71 and older consume 1200 mg/day of calcium.
- Intakes in excess of 1200 to 1500 mg/day may increase the risk of developing kidney stones, cardiovascular disease, and stroke.

VIT D

- 800 to 1000 international units (IU) of vitamin D per day for adults age 50 and older.
- **Treatment of vitamin D deficiency-**
Adults should be treated with 50,000 IU once a week or the equivalent daily dose (7000 IU vitamin D₂ or vitamin D₃) for 8–12 weeks to achieve a 25(OH)D blood level of *approximately 30 ng/ml*.

This regimen should be followed by maintenance therapy of 1500–2000 IU/day.

Dororučené dávky vápníku (FDA)

Děti	6-10	800-1200 mg
	11-24	1200-1500 mg
Muži	25-65	1000 mg
	Nad 65	1500 mg
Ženy	25 –menopauza	1000 mg
	Po menopauze	1500 mg
	Kojící a gravidní	1200-1500 mg
	Osteoporóza	1500 mg

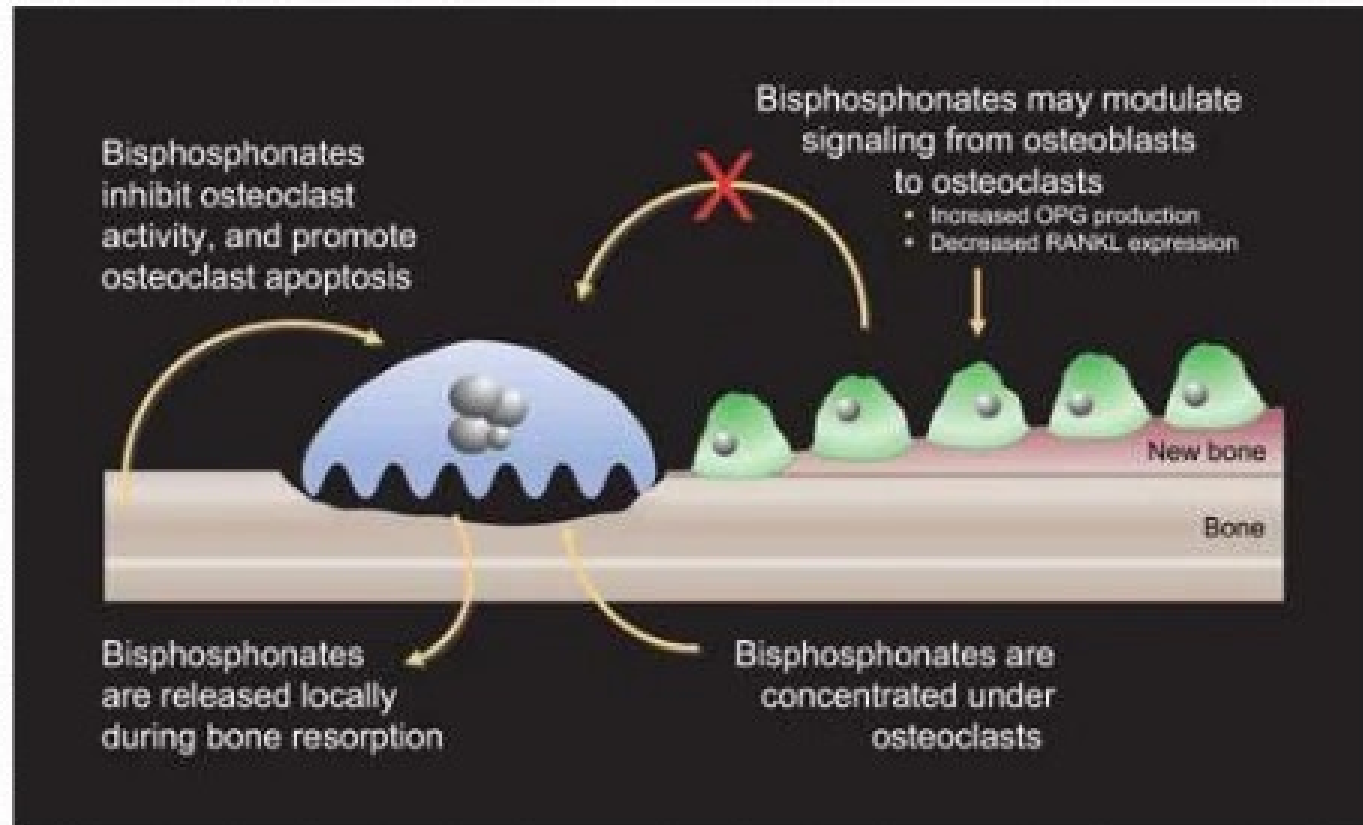
Who should be considered for treatment?

Postmenopausal women and men age 50 and older presenting with the following should be considered-

- **A hip or vertebral fracture** (clinically apparent or found on vertebral imaging).
- T-score ≤ -2.5 at the femoral neck, total hip, or lumbar spine.
- Low bone mass (T-score between -1.0 and -2.5 at the femoral neck or lumbar spine)
- a 10-year probability of a hip fracture $\geq 3\%$ or a 10-year probability of a major osteoporosis-related fracture $\geq 20\%$.

Bisphosphonates

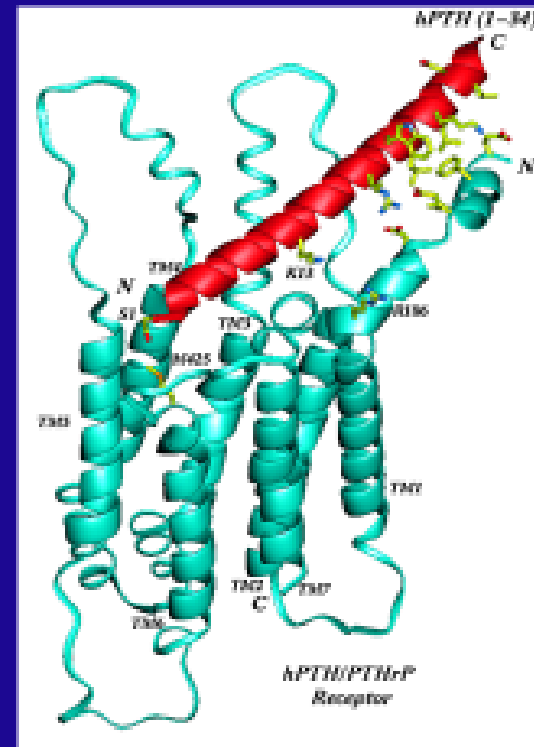
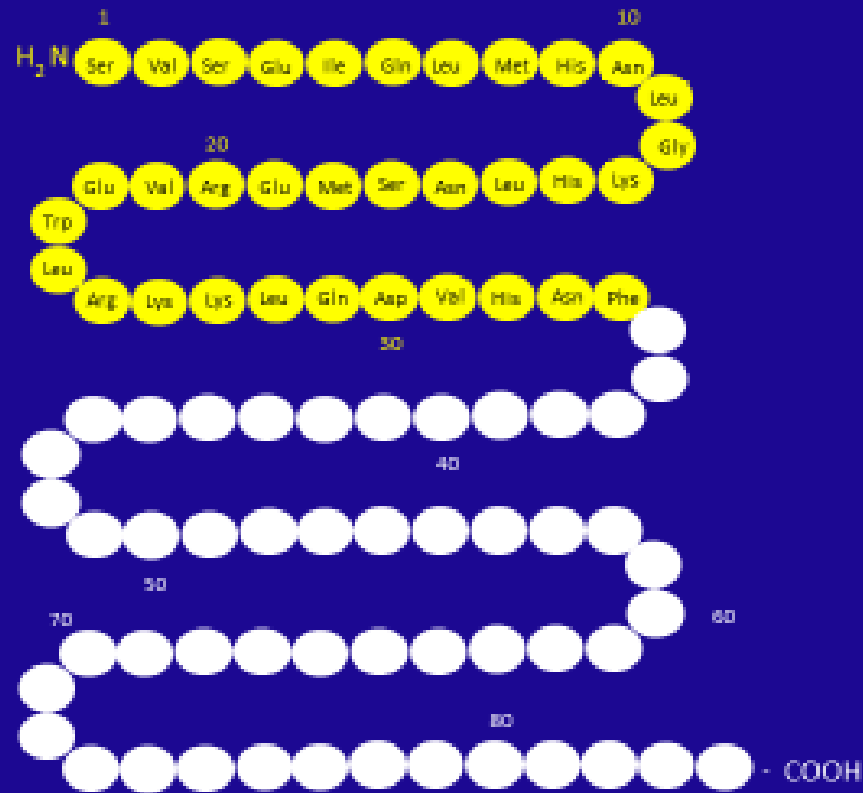
- Are analogues of pyrophosphates.
- MOA- attach to bone remodelling sites.
- Cause apoptosis of osteoclasts by by disrupting cytoskeleton.



PTH, teriparatide

- Teriparatide is approved for the treatment of osteoporosis in postmenopausal women and men at high risk for fracture.
- It is also approved for treatment in men and women at high risk of fracture with osteoporosis associated with **sustained systemic glucocorticoid therapy.**
- DOSE-20 µg daily subcutaneous injection.
- Duration not to exceed 18 to 24 months.

Lidský PTH 1-34 a 1-84



hPTH 1-84
(crystal structure)

Adapted from Niall, et al. Proc Natl Acad Sci USA 1974;71:384
Adapted from Jin, et al. J Biol Chem 2000;33:27238

PTH Efficacy

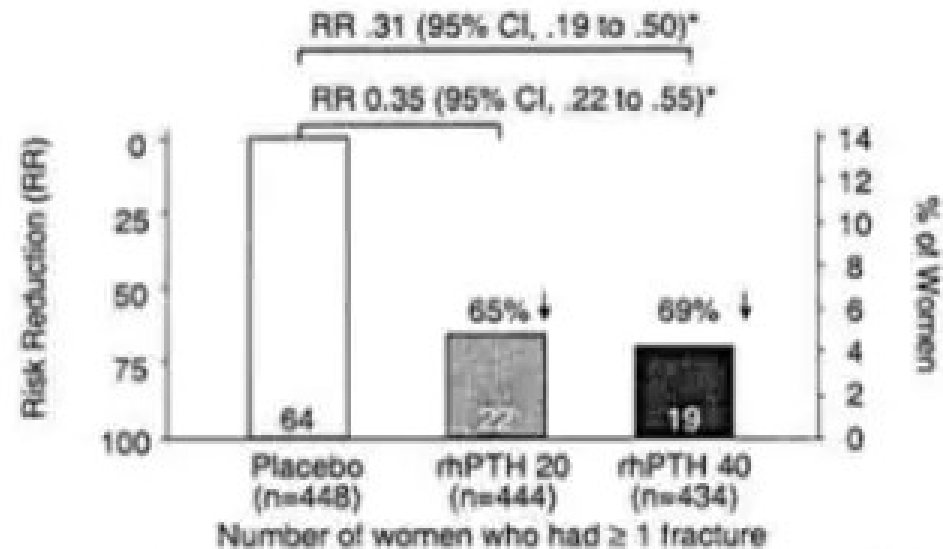
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Effect of rhPTH (1-34) on the Risk of New Vertebral Fractures



Neer RM, et al. *N Engl J Med*. 2001;344(19):1434-1441

*P < .001 vs Placebo

G.DONESUMAB[RANKL INHIBITOR]-

- Dose-60mg/6months S.C
- Used in postmenopausal women.
- Side effects-hypocalcemia , cellulitis ,skin rash.

