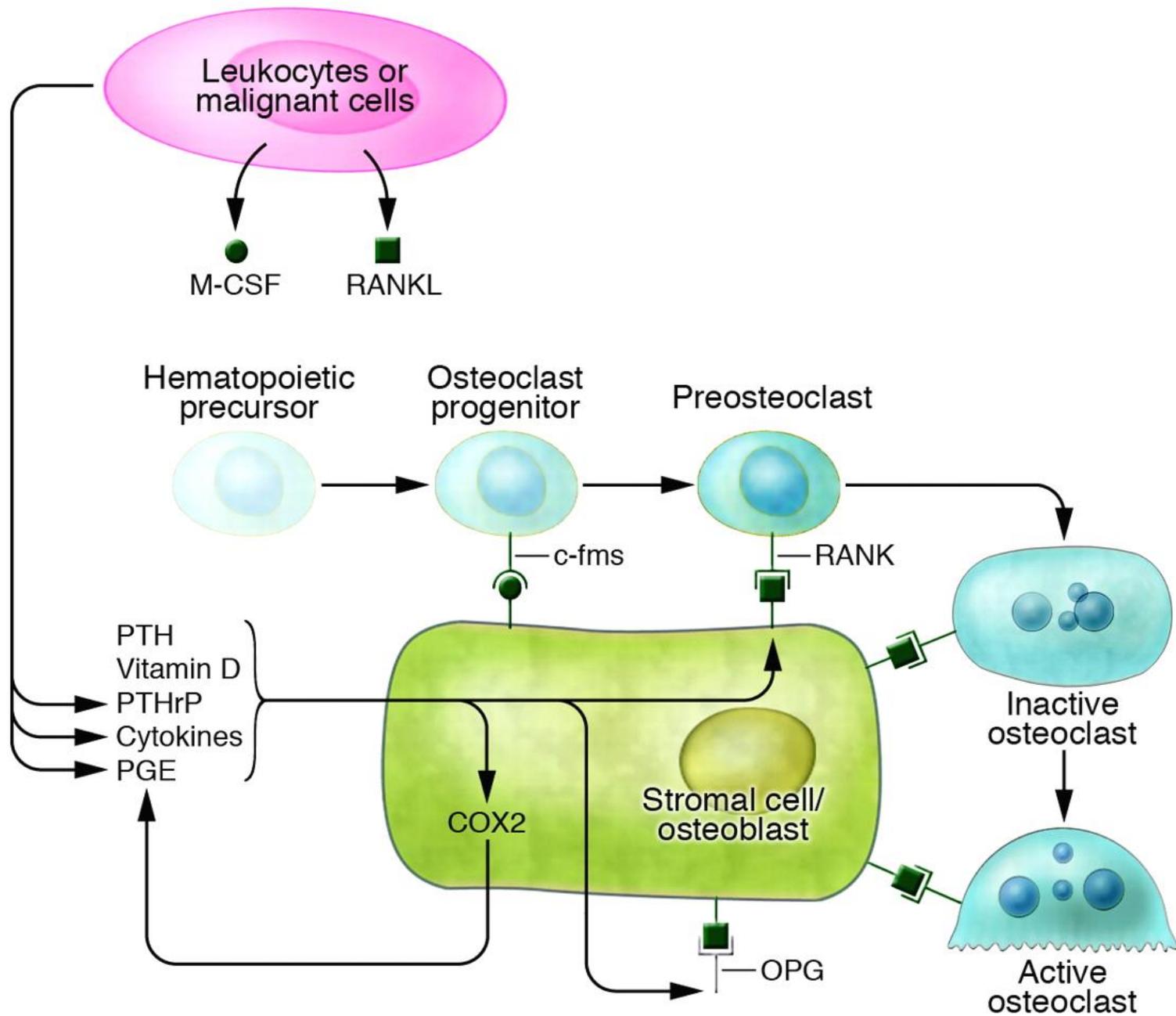


Osteoporosis, osteodystrophy and osteomalacia. Bone state in patients with chronic renal failure

TZKM 7. 4. 2017

Bone remodeling

- ❑ **Osteoclast activation**
 - ❑ **Resorption phase-** due to osteoclast activation- short period
 - ❑ **Reverse phase-** bone surface is covered by mononuclear cell
 - ❑ **Formation phase-** osteoblast production in bone matrix - long.
-



Bone remodelling - final evaluation as physiological state of the bone

- Equilibrium between osteoclastic and osteoblastic activities chronically
 - Adequate time remodelling in dependence on mechanic powers necessities
-

Bone properties

- Bones must be stiff so that they do not bend when loaded.
 - Bones must also be flexible so they can absorb the energy imposed by loading as potential energy by elastic then plastic deformation. Structural failure may occur if bones deform too little or too much.
 - Age- and menopause-related abnormalities in bone remodeling produce loss of material and structural properties.
 - High remodeling reduces the mineral content of bone, resulting in loss of stiffness.
 - Sex hormone deficiency increases the volume of bone resorbed and reduces the volume of bone formed in each BMU. The contributions made by differences
 - in material composition, tissue mineral content, collagen type and cross-linking)
 - structure (bone size, cortical thickness and porosity, trabecular number, thickness, connectivity), and
 - other factors (microdamage burden, osteocyte density) to sex and racial differences in bone fragility remain poorly defined.
-

Skeletal fragility

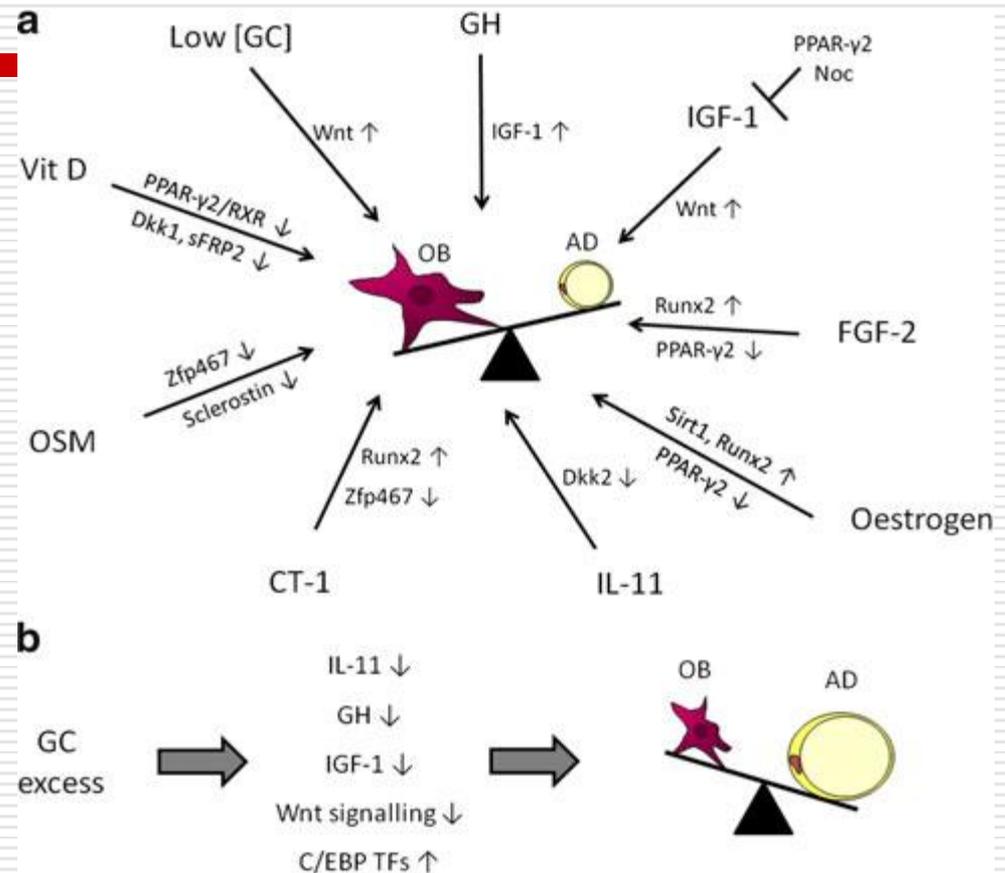
Skeletal fragility can result from:

- ❑ 1. failure to produce a skeleton of optimal mass and strength during growth
 - ❑ 2. excessive bone resorption resulting in decreased bone mass and microarchitectural deterioration of the skeleton; and an inadequate formation response to increased resorption during bone remodeling.
 - ❑ In addition, the incidence of fragility fractures, particularly of the hip and wrist, is further determined by the frequency and direction of falls.
-

Equilibrium between osteoblastogenesis (OB) and adipogenesis (AD)

- a) Several endogenous factors support osteoblastogenesis against adipogenesis.
- b) High levels of cortisol prefer adipogenesis to osteoblastogenesis

Low [GC] low (physiological) concentrations of glucocorticoids, GH-growth hormone, IGF-1 insulin-like growth factor-1, FGF-2 fibroblast growth factor-2, IL-11 interleukin-11, CT-1 cardiotrophin-1, OSM oncostatin M, OB osteoblast, AD-adipocyte

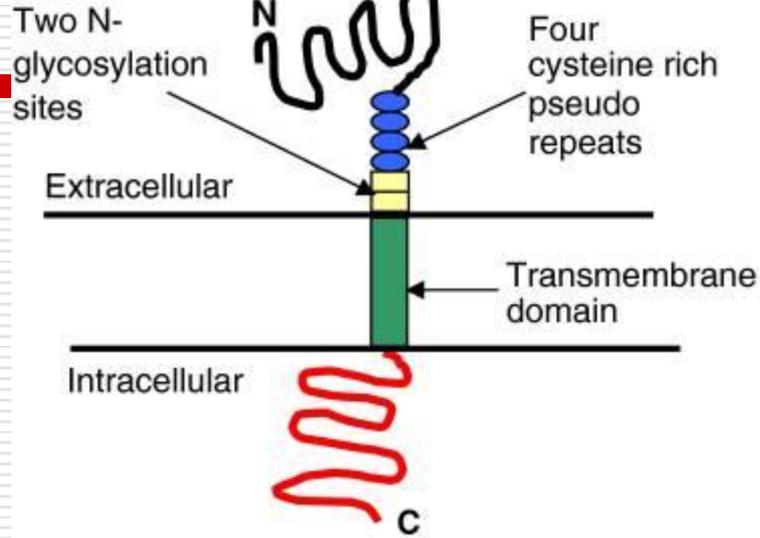


Alterations of bone remodelling

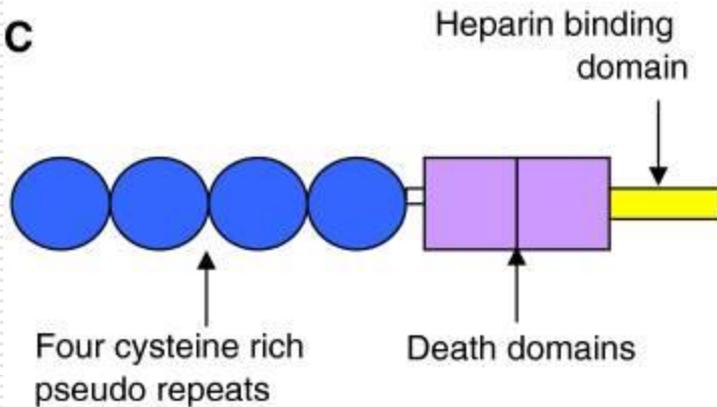
- Metabolic bone diseases:
 - **Osteoporosis** (chronic predominance of osteoclastic above osteoblastic activities)
 - **Osteodystrophy** (increased bone remodelling rate)
 - **Rickets/osteomalacia** (decreased bone remodelling rate)
-

RANK

A

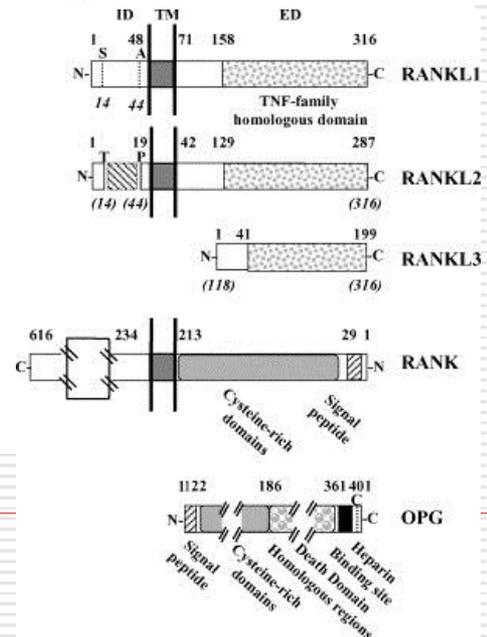
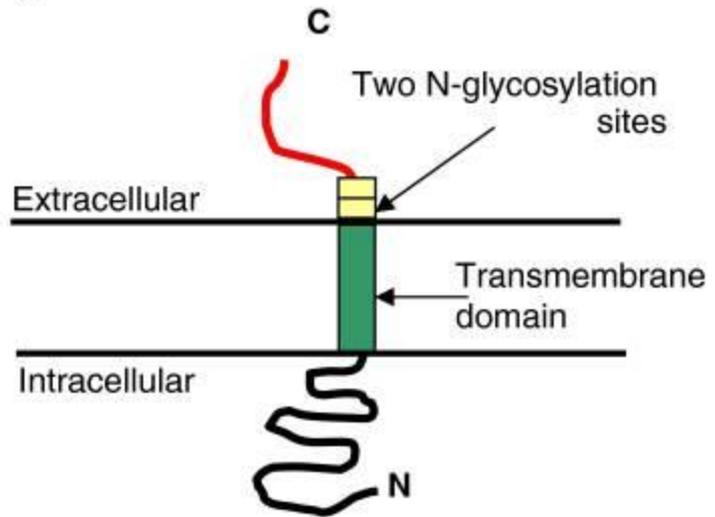


C



Osteoprotegerin

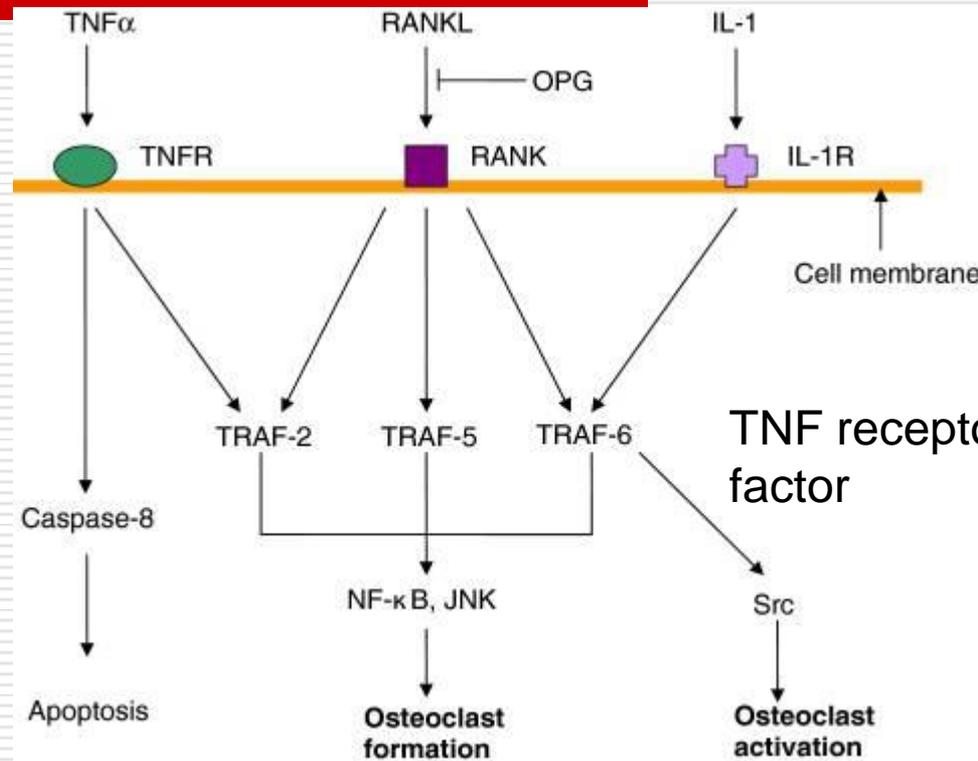
RANKL



OPG/RANK/RANKL as a common effector in bone immune system and a vascular system (to the previous figure)

- ❑ OPG, RANK and RANKL are selectively produced by many cell types in different tissues: lymphocytes, osteoblasts and endothelial cells.
 - ❑ RANKL is functioning as a survival factor for dendritic cells and as an osteoclastogenic factor after RANK ligation.
 - ❑ OPG inhibits osteolysis and blocks RANKL/RANK interaction.
 - ❑ OPG/RANKL/RANK triad is considered an osteoimmunomodulating complex.
-

RANK-RANKL signální cesta, inhibice vazby RANK-RANKL osteoprotegerinem (OPG)



Metabolic bone diseases

- Osteoporosis
 - Osteodystrophy
 - Osteomalacia (rickets in childhood)
-

Osteoporosis

- ❑ Osteoporosis remains the most common metabolic abnormality of bone. It has been described as “a silent epidemic” affecting one in two women and one in five men, older than 50 years of age, during their lifetime.
 - ❑ It is now defined as a systemic skeletal disease characterized by low bone mass and micro-architectural deterioration of bone resulting in fractures with little or no trauma.
-

Osteoporosis



Normal



Osteoporotic bone

© Steiner 2004

Osteoporosis

- is a skeletal disease characterised by low bone mass and microarchitectural deterioration with a resulting increase in bone fragility and hence susceptibility to fracture.
 - It is an important public health issue because of the potentially devastating results and **high cumulative rate of fractures.**
-

Osteoporosis - causes

- Insufficiency of estrogens
 - Age (both men and women)
 - Immobilisation
 - Increased levels of glucocorticoids
 - Decreased levels of vitamin K2
-

Osteoporosis

- ❑ Oestrogen has a central role in normal physiological remodelling, and oestrogen deficiency after the menopause results in a remodelling imbalance with a substantial increase in bone turnover.
 - ❑ This imbalance leads to a progressive loss of trabecular bone, partly because of increased osteoclastogenesis.
 - ❑ Enhanced formation of functional osteoclasts seems to be the result of increased elaboration of osteoclastogenic proinflammatory cytokines such as interleukin-1 and tumour necrosis factor, which are negatively regulated by oestrogen.
 - ❑ A direct effect of oestrogen in accelerating osteoclast apoptosis has also been attributed to increased production of transforming growth factor β .
-

Etiopathogenesis of osteoporosis

- ❑ Osteoporosis is likely to be caused by complex interactions among local and systemic regulators of bone cell function.
 - ❑ The heterogeneity of osteoporosis may be due not only to differences in the production of systemic and local regulators, but also to changes in receptors, signal transduction mechanisms, nuclear transcription factors, and enzymes that produce or inactivate local regulators.
 - ❑ Since the first human osteoporosis study indicated an association among bone mass, fragility, and polymorphisms in the *vitamin D receptor (VDR)* gene, more than 30 candidate genes have been reported that might influence skeletal mass and fragility.
 - ❑ Since osteoporosis is a complex, polygenic disorder, the contributions of specific gene polymorphisms are likely to be relatively small, but may still be clinically important.
-

Estrogen deficiency

- ❑ Fracture risk is inversely related to estrogen levels in postmenopausal women.
 - ❑ Recent studies in humans have shown that the level of estrogen required to maintain relatively normal bone remodeling in older postmenopausal women is lower than that required to stimulate classic target tissues such as the breast and uterus.
 - ❑ As little as one-quarter of the dose of estrogen that stimulates the breast and uterus is sufficient to decrease bone resorption and increase bone mass in older women. This greater sensitivity of the skeleton may be age related.
-

Estrogen influence on bone state

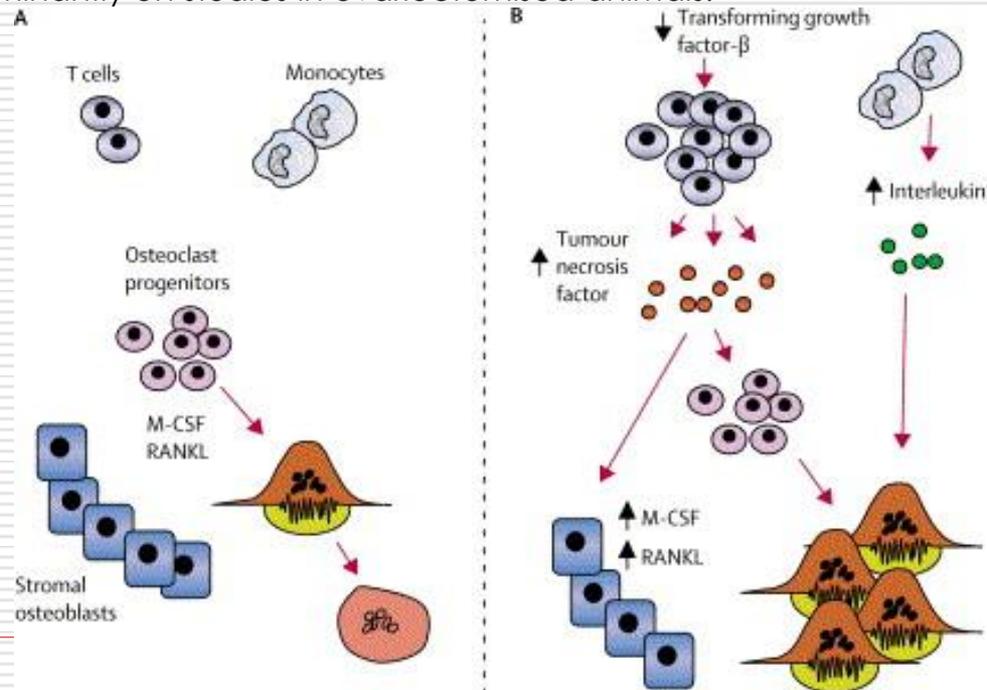
- ❑ Estrogen is critical for epiphyseal closure in puberty in both sexes and regulates bone turnover in men as well as women.
 - ❑ In fact, estrogen has a greater effect than androgen in inhibiting bone resorption in men, although androgen may still play a role.
 - ❑ Estrogen may also be important in the acquisition of peak bone mass in men.
 - ❑ Osteoporosis in older men is more closely associated with low estrogen than with low androgen levels.
-

Central role of estrogen deficiency

- The concept that estrogen deficiency is critical to the pathogenesis of osteoporosis was based initially on the fact that postmenopausal women, whose estrogen levels naturally decline, are at the highest risk for developing the disease. Morphologic studies and measurements of certain biochemical markers have indicated that bone remodeling is accelerated at the menopause, as both markers of resorption and formation are increased.
 - Now, an increase in bone resorption, and not impaired bone formation, appears to be the driving force for bone loss in the setting of estrogen deficiency. But the rapid and continuous bone loss that occurs for several years after the menopause must indicate an impaired bone formation response, since in younger individuals going through the pubertal growth spurt, even faster rates of bone resorption can be associated with an increase in bone mass. However, the increased bone formation that normally occurs in response to mechanical loading is diminished in estrogen deficiency, suggesting estrogen is both anti-catabolic and anabolic.
-

A: Oestrogen replete state. Osteoclasts are formed by interaction between macrophagic, monocytic precursor cells and cells of the osteoblast lineage, but might also be initiated by inflammatory cells, especially T cells. Osteoclasts express receptor activator of NF κ B (RANK). The RANK ligand (RANKL) enhances each of these steps whereas osteoprotegerin, a decoy receptor, blocks this interaction.

B: Oestrogen deficient state. Important bone sparing effects of oestrogen take place via **modulation of bone cell lifespan and reduced cytokine-driven osteoclastogenesis**. In the absence of oestrogen, the pool of T cells secreting tumour necrosis factor is expanded through a mechanism involving reduced transforming growth factor β . Additionally, monocytes secrete increased amounts of interleukin-1. Tumour necrosis factor stimulates M-CSF (macrophage colony-stimulating factor) and RANKL production and acts on osteoclast progenitors primed by RANKL, to heighten osteoclast generation. RANKL and interleukin-1 also act to increase osteoclast survival by preventing apoptosis. As a result, in oestrogen deficiency, the number of functional basic multicellular units in bone is substantially increased. This model is based predominantly on studies in ovariectomised animals.



Osteoporosis

- ❑ Osteoporotic fractures result from a **combination of reduced bone strength and increased rate of falls**. Although bone mineral density remains the best available non-invasive assessment of bone strength in routine clinical practice, many other skeletal characteristics also contribute to bone strength.
 - ❑ These include bone macroarchitecture (shape and geometry), bone microarchitecture (both trabecular and cortical), matrix and mineral composition, as well as the degree of mineralisation, microdamage accumulation, and the rate of bone turnover, which can affect the structural and material properties of bone.
-

Common adverse effects of glucocorticoid therapy- **glucocorticoid-induced osteoporosis**

- ❑ Glucocorticoid-induced osteoporosis is the most common type of iatrogenic osteoporosis and a frequent cause of secondary osteoporosis.
 - ❑ An estimated 50% of patients taking glucocorticoids for longer than 6 months will develop secondary osteoporosis .
 - ❑ The absolute risk for glucocorticoid-induced osteoporosis is higher in patients aged 65 years or older given their baseline age-related fracture risk, although the relative risk of fracture related to glucocorticoid use may be even higher in patients under 65 .
-

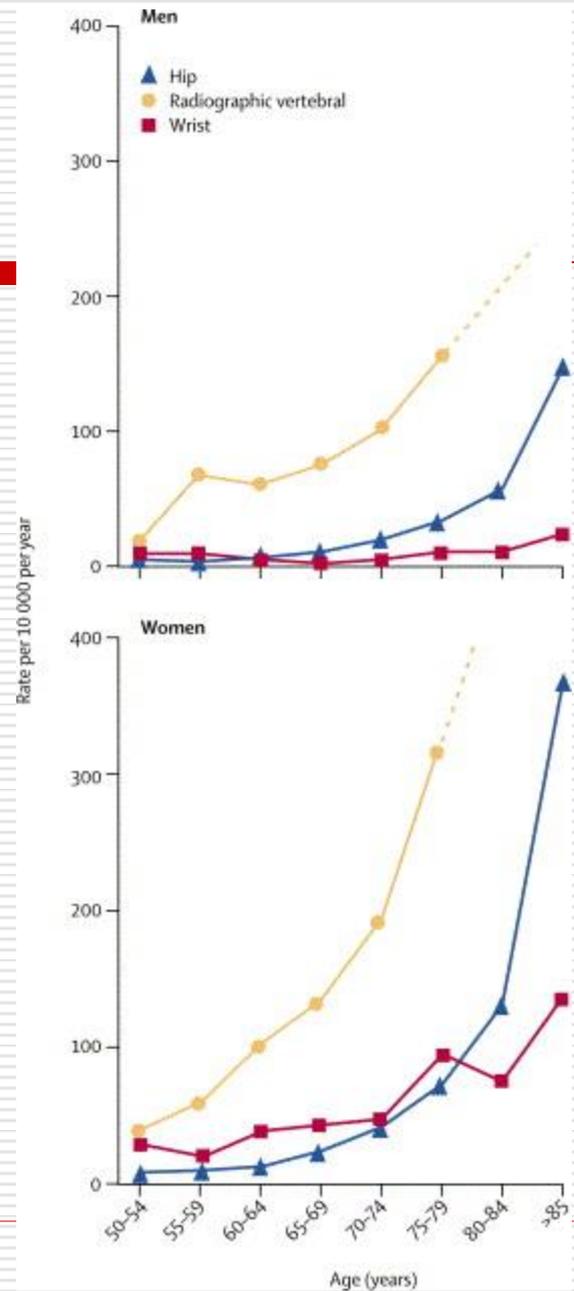
Common adverse effects of glucocorticoid therapy

- ❑ There is substantial and accelerated decreases in bone mineral density (BMD) with oral glucocorticoid therapy, most pronounced in the first year, with trabecular bone more quickly affected than cortical bone.
 - ❑ Even after only 2 months of high-dose glucocorticoids, studies show markedly decreased BMD at the lumbar spine, femoral neck and whole body, with the greatest loss in the trabecular lumbar vertebrae.
 - ❑ In light of the high incidence of glucocorticoid-induced osteoporosis and associated fractures, screening and treatment rates for glucocorticoid-induced osteoporosis has come under substantial scrutiny.
 - ❑ Less than 50% of patients receiving long-term glucocorticoids have been evaluated for osteoporosis, and less than 25% have been treated. There is great variability among clinicians in both the awareness of glucocorticoid-induced osteoporosis and the importance of prevention and treatment as the standard of care.
 - ❑ The use of antiosteoporotic medication was observed to be most common among postmenopausal women, where it approached **50%**.
-

Osteoporosis induced by cortisol

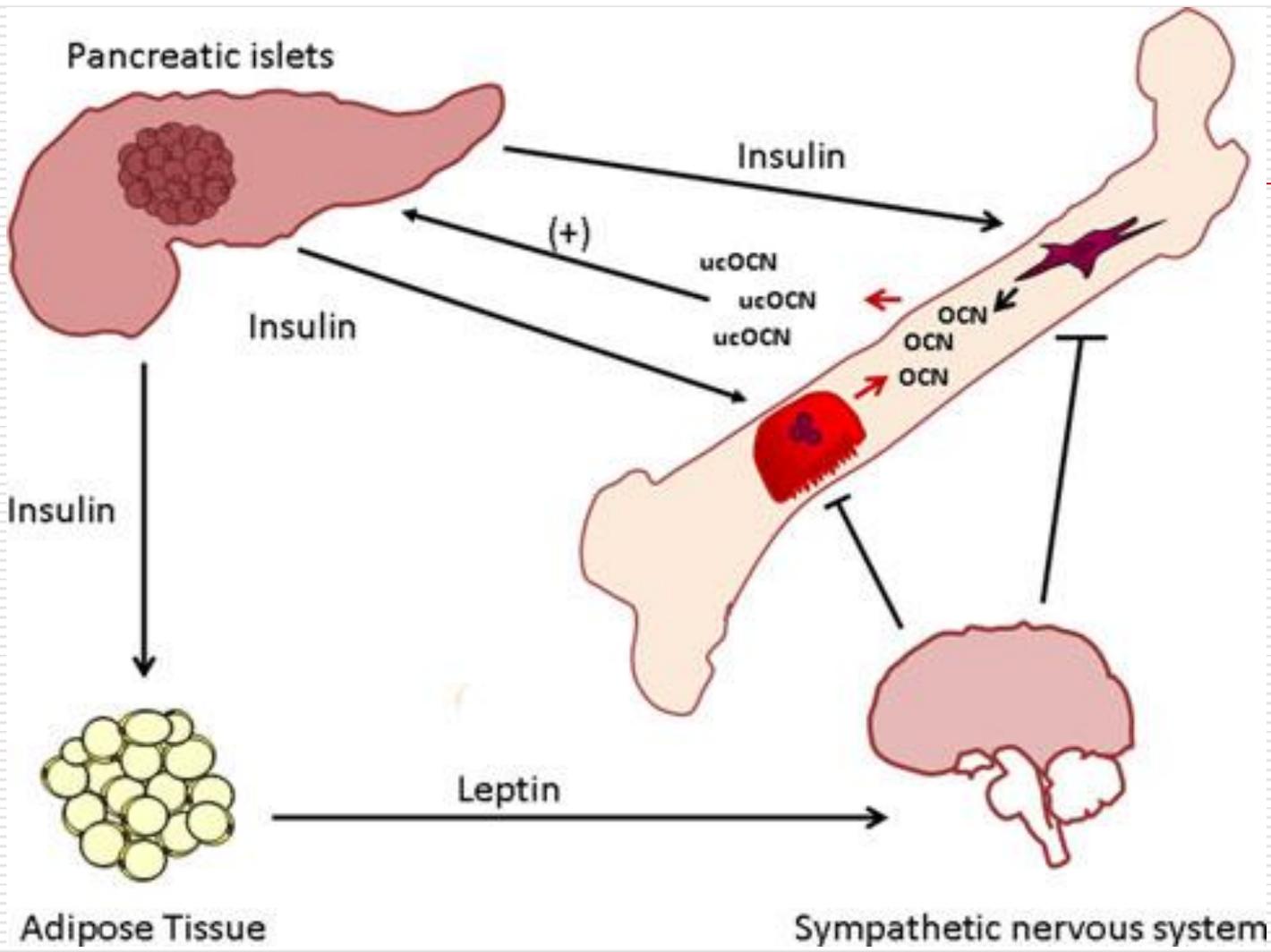
- ❑ Cortisol modifies proliferative and metabolic activities of bone cells
 - ❑ Cortisol inhibits osteoblastogenesis
 - ❑ Reduces half-life time of osteoblasts which is leading to decreased bone formation
-

Age-specific and sex-specific incidence of radiographic vertebral, hip, and distal forearm fractures
Data derived from European Prospective Osteoporosis Study and General Practice Research Database.

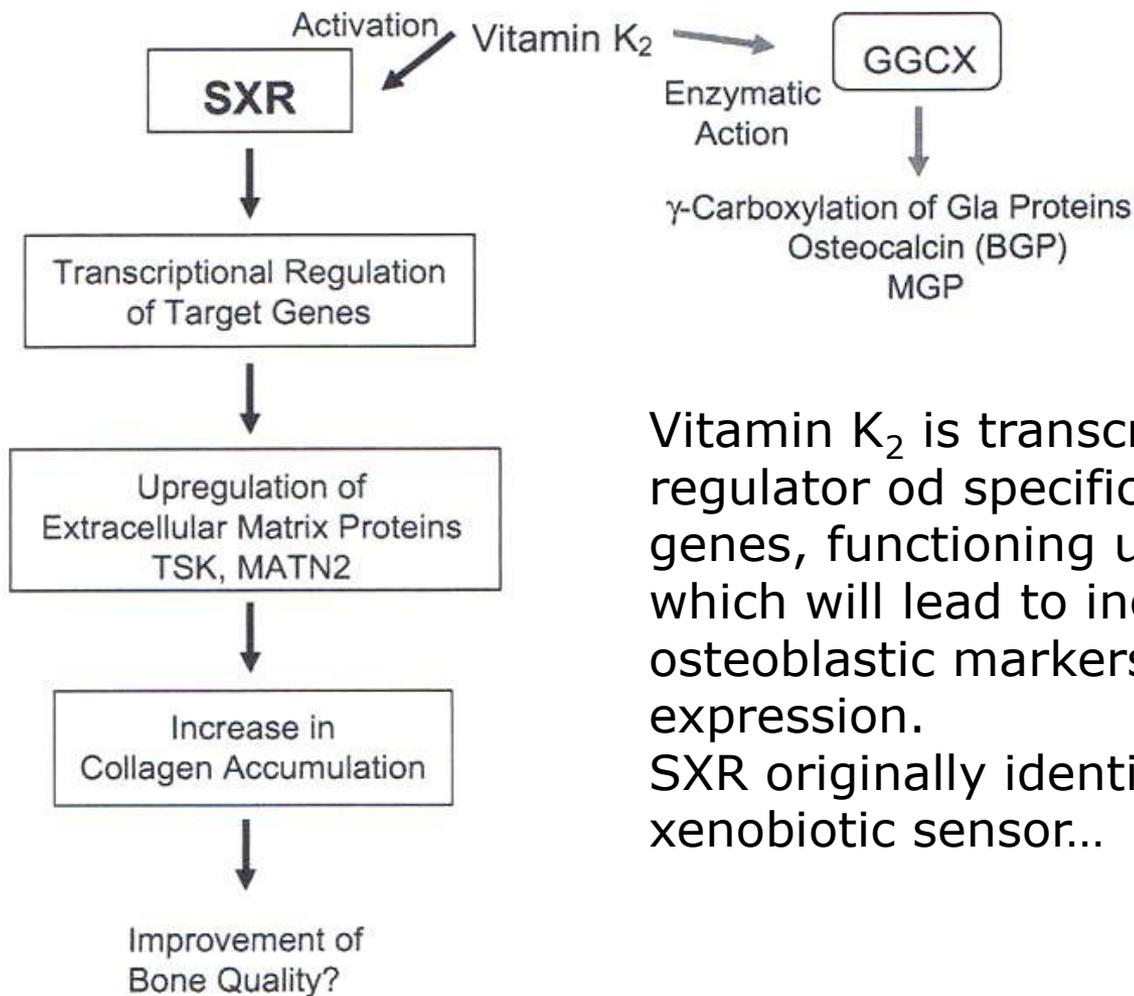


Vitamin K and bones

- Vitamin K₂ is substantial cofactor for γ -carboxylase, enzyme which catalyses conversion of specific residuals of glutamic acid to Gla residuals
 - Vitamin K₂ is necessary for γ -carboxylation of proteins of bone matrix which contain Gla as **MGP (= matrix Gla protein) a osteocalcin.**
 - Uncompleted γ -carboxylation of osteocalcin and MGP during vitamin K decrease lead to osteoporosis and high risk of fractures. Vitamin K₂ stimulates synthesis of osteoblastic markers and bone deposition.
 - Vitamin K₂ decreases bone reabsorption by inhibition of osteoclasts formation and by decrease of their resorption activity.
 - Vitamin K₂ treatment induces osteoclast apoptosis, but inhibits osteoblasts apoptosis which is leading to increased bone formation.
 - Vitamin K₂ supports osteocalcin expression (increases its mRNA) which can be further modulated by 1, 25-(OH)₂ vitamin D₃.
-



Cortisol generally antagonizes insulin ...



Vitamin K₂ is transcription regulator of specific bone genes, functioning using SXR which will lead to increase of osteoblastic markers expression. SXR originally identifies as xenobiotic sensor...

Fig. 3. SXR- and vitamin K₂-dependent regulatory mechanisms of bone metabolism in osteoblastic cells. SXR promotes collagen accumulation in osteoblastic cells by regulating the transcription of its target genes including those encode extracellular matrix proteins. Vitamin K₂ plays a role in the posttranslational modification of Gla proteins by functioning as a coenzyme of γ -glutamyl carboxylase (GGCX) and also acts as a potent SXR ligand in bone metabolism

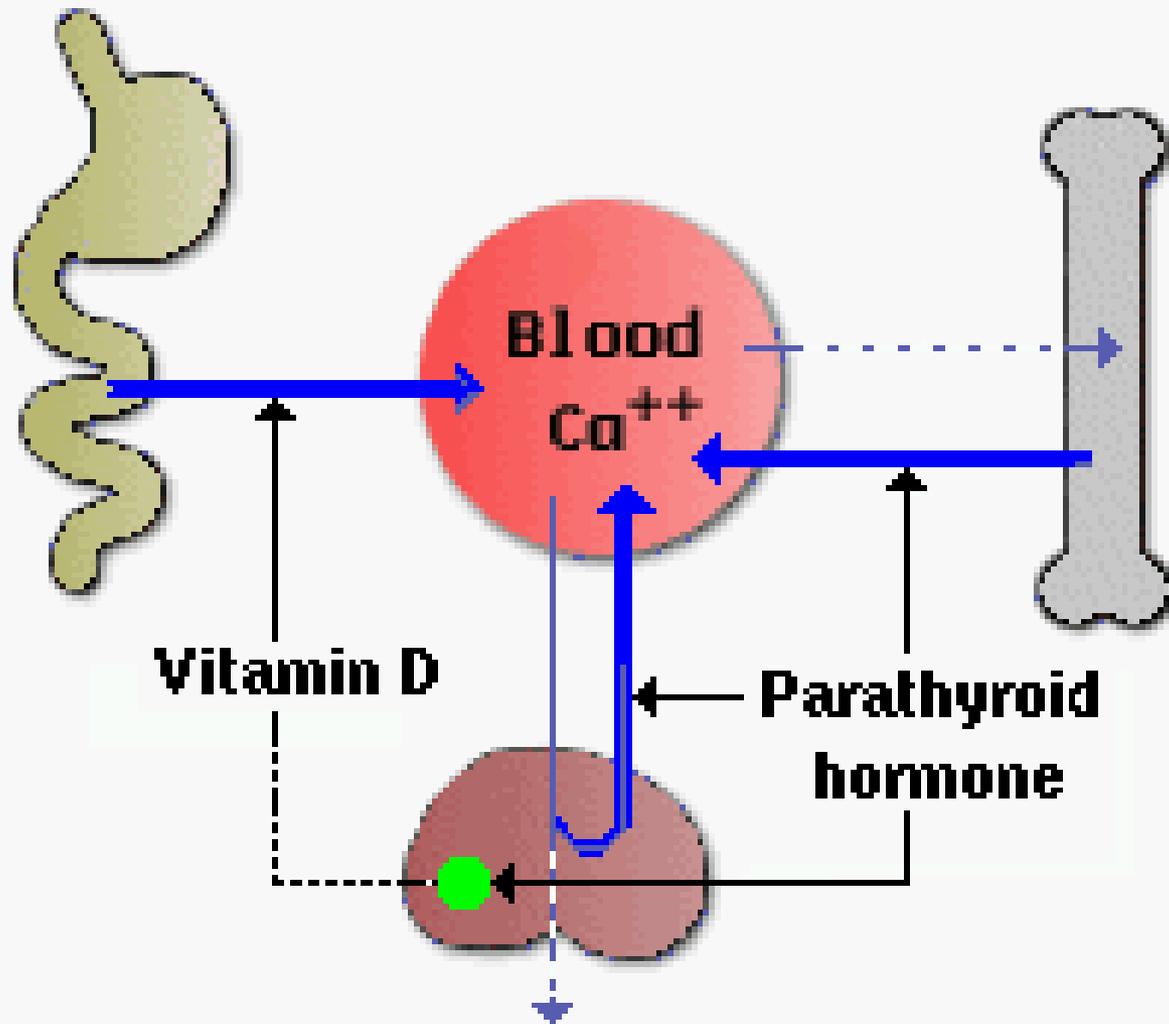
Recommended therapy of osteoporosis

| | Vertebral fracture | Hip fracture | Non-vertebral fracture |
|------------------------------------|--------------------|--------------|------------------------|
| Bisphosphonate | | | |
| Alendronate | A | A | A |
| Risedronate | A | A | A |
| Etidronate | A | C | C |
| Hormone replacement therapy | A | A | A |
| SERM (Raloxifene) | A | C | C |
| Calcitonin, intranasal | A | C | C |
| Teriparatide | A | - | A |
| Calcium and vitamin D preparations | | | |
| Vitamin D monotherapy | C | C | C |
| Calcium monotherapy | B | C | C |
| Vitamin D plus calcium | C | A | A |

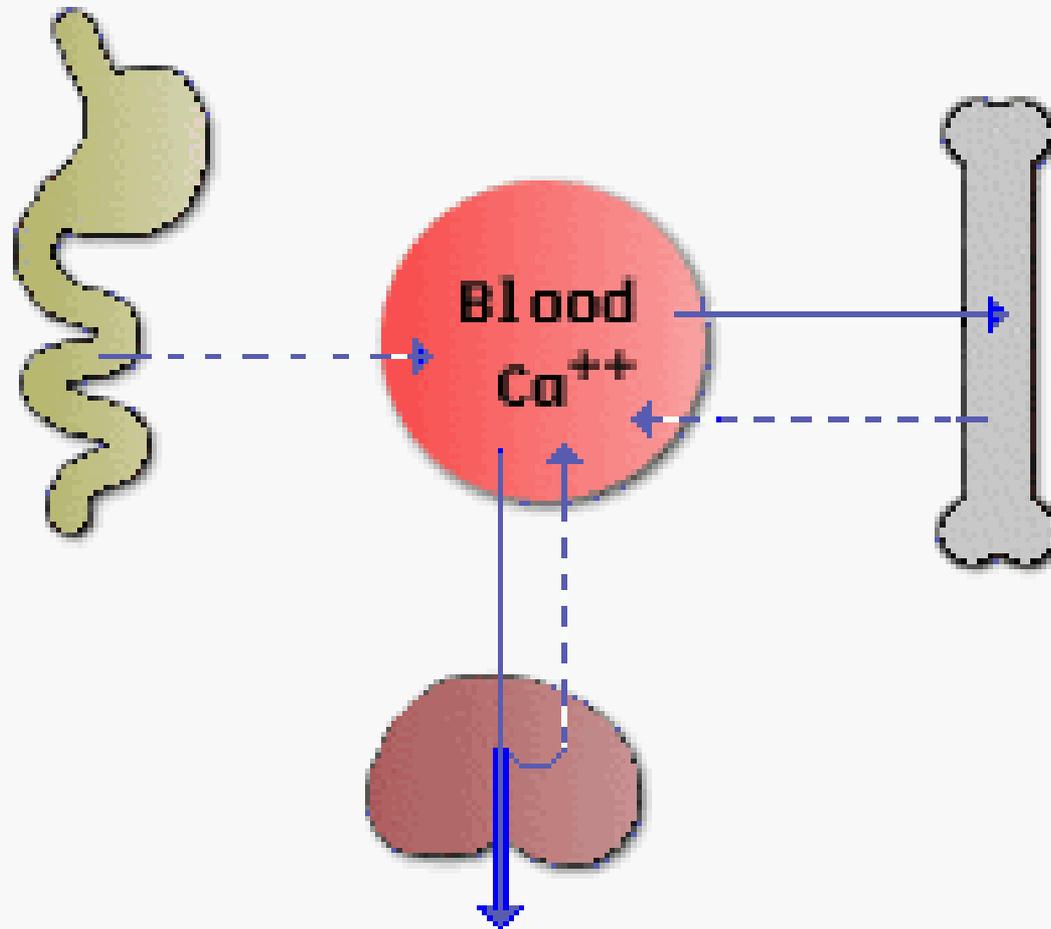


^{99m}Tc -Technetium-hydroxymethylene diphosphonate bone scintigraphy. The scan is typical for a bone metabolic disease, even though, in theory, any foci could correspond to a primary bone tumor. The FDG PET/CT study ruled out the hypothesis.

Calcium deficiency in blood



Calcium overload in blood



Calcium, vitamin D, and parathyroid hormone

- The active 1,25 dihydroxy vitamin D (calcitriol), is not only necessary for optimal intestinal absorption of calcium and phosphorus, but also exerts a tonic inhibitory effect on parathyroid hormone (PTH) synthesis, so that there are dual pathways that can lead to secondary hyperparathyroidism.
 - Vitamin D deficiency and secondary hyperparathyroidism can contribute not only to accelerated bone loss and increasing fragility, but also to neuromuscular impairment that can increase the risk of falls.
-

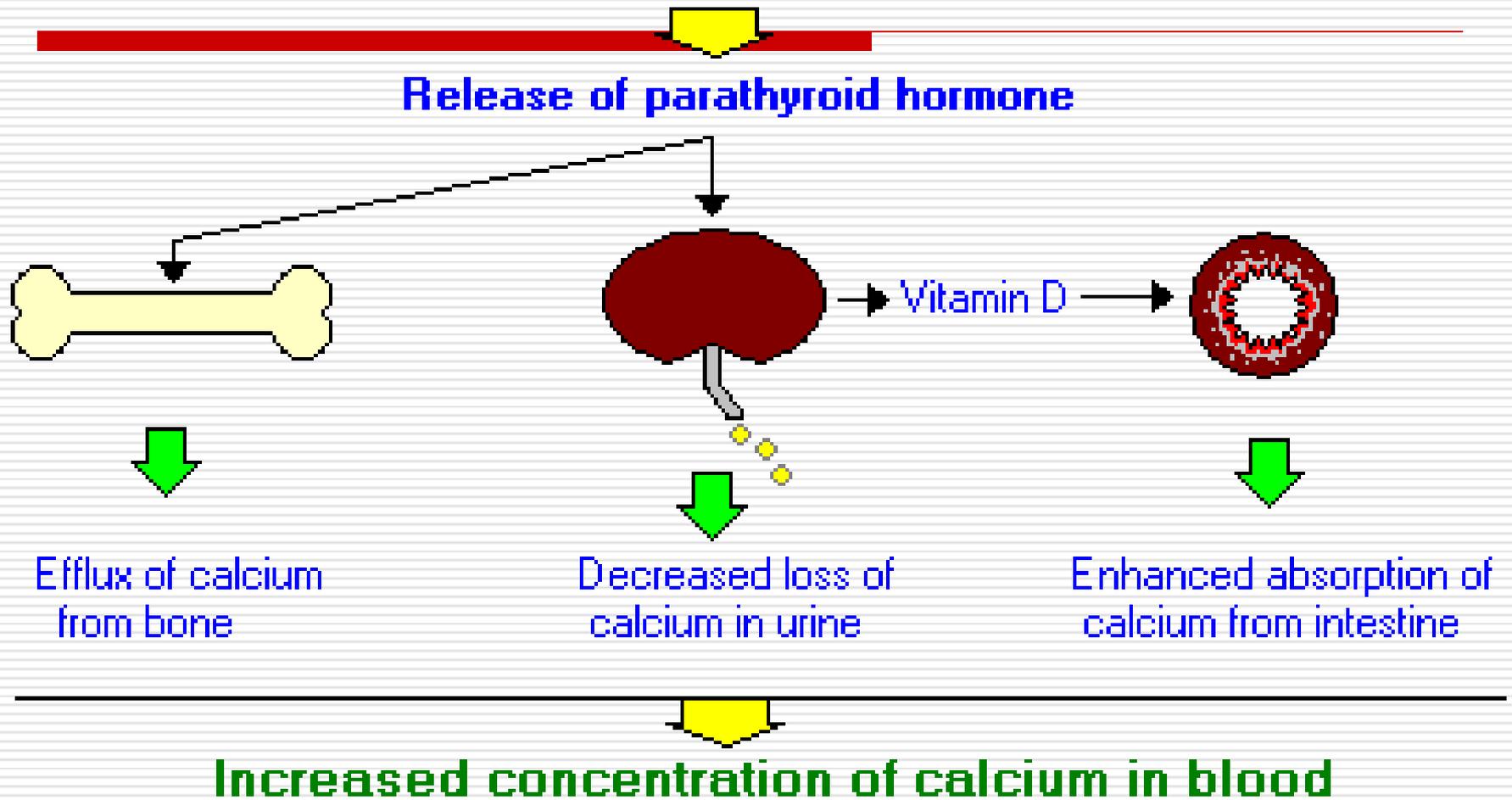
| | Calcium Deprivation | Calcium Loading |
|----------------------------|--|---|
| Parathyroid hormone | Secretion stimulated | Secretion inhibited |
| Vitamin D | Production stimulated by increased parathyroid hormone secretion | Synthesis suppressed due to low parathyroid hormone secretion |

| | | |
|---|---|--|
| Calcitonin | Very low level secretion | Secretion stimulated by high blood calcium |
| Intestinal absorption of calcium | Enhanced due to activity of vitamin D on intestinal epithelial cells | Low basal uptake |
| Release of calcium and phosphate from bone | Stimulated by increased parathyroid hormone and vitamin D | Decreased due to low parathyroid hormone and vitamin D |
| Renal excretion of calcium | Decreased due to enhanced tubular reabsorption stimulated by elevated parathyroid hormone and vitamin D; hypocalcemia also activates calcium sensors in loop of Henle to directly facilitate calcium reabsorption | Elevated due to decreased parathyroid hormone-stimulated reabsorption. |
| Renal excretion of phosphate | Strongly stimulated by parathyroid hormone; this phosphaturic activity prevents adverse effects of elevated phosphate from bone resorption | Decreased due to hypoparathyroidism |
| General Response | Typically see near normal serum concentrations of calcium and phosphate due to compensatory mechanisms. Long term hypocalcemia leads to osteopenia/osteoporosis | Low intestinal absorption and enhanced renal excretion guard against development of hypercalcemia. |

Hormonal calcium control systems

- Maintaining normal blood calcium and phosphorus concentrations is managed through the concerted action of three hormones that control fluxes of calcium in and out of blood and extracellular fluid:
 - *Parathyroid hormone* serves to increase blood concentrations of calcium.
 - Mechanistically, parathyroid hormone preserves blood calcium by several major effects:
 - Stimulates production of the biologically-active form of vitamin D within the kidney.
 - Facilitates mobilization of calcium and phosphate from bone. To prevent detrimental increases in phosphate, parathyroid hormone also has a potent effect on the kidney to eliminate phosphate (phosphaturic effect).
 - Maximizes tubular reabsorption of calcium within the kidney. This activity results in minimal losses of calcium in urine.
-

Low concentration of calcium in blood



Control of parathyroid hormone secretion

Parathyroid hormone is released in response to low extracellular concentrations of free calcium.

Changes in blood phosphate concentration can be associated with changes in parathyroid hormone secretion, but this appears to be an indirect effect and phosphate per se is not a significant regulator of this hormone.

When calcium concentrations fall below the normal range, there is a steep increase in secretion of parathyroid hormone.

Low levels of the hormone are secreted even when blood calcium levels are high. The figure to the right depicts parathyroid hormone release from cells cultured in vitro in differing concentrations of calcium.

The parathyroid cell monitors extracellular free calcium concentration via an integral membrane protein that functions as a [calcium-sensing receptor](#).

Disease states due to hyperthyroidism- osteodystrophies

- (Both increased and decreased secretion of parathyroid hormone are recognized as causes of serious disease in man).
 - **Excessive secretion of parathyroid hormone is seen in two forms:**
 - *Primary hyperparathyroidism* is the result of parathyroid gland disease, most commonly due to a parathyroid tumor (adenoma) which secretes the hormone without proper regulation. Common manifestations of this disorder are chronic elevations of blood calcium concentration (hypercalcemia), kidney stones and remodeling of bone.
-

Disease states due to hyperthyroidism- renal osteodystrophy

- *Secondary hyperparathyroidism* is the situation where disease outside of the parathyroid gland leads to excessive secretion of parathyroid hormone. A common cause of this disorder is kidney disease - if the kidneys are unable to reabsorb calcium, blood calcium levels will fall, stimulating continual secretion of parathyroid hormone to maintain normal calcium levels in blood. Secondary hyperparathyroidism can also result from inadequate nutrition - for example, diets that are deficient in calcium or vitamin D, or which contain excessive phosphorus (e.g. all meat diets for carnivores). A prominent effect of secondary hyperparathyroidism is remodeling of bone, leading to pathologic fractures or "rubber bones".

Disease states due to hypoparathyroidism

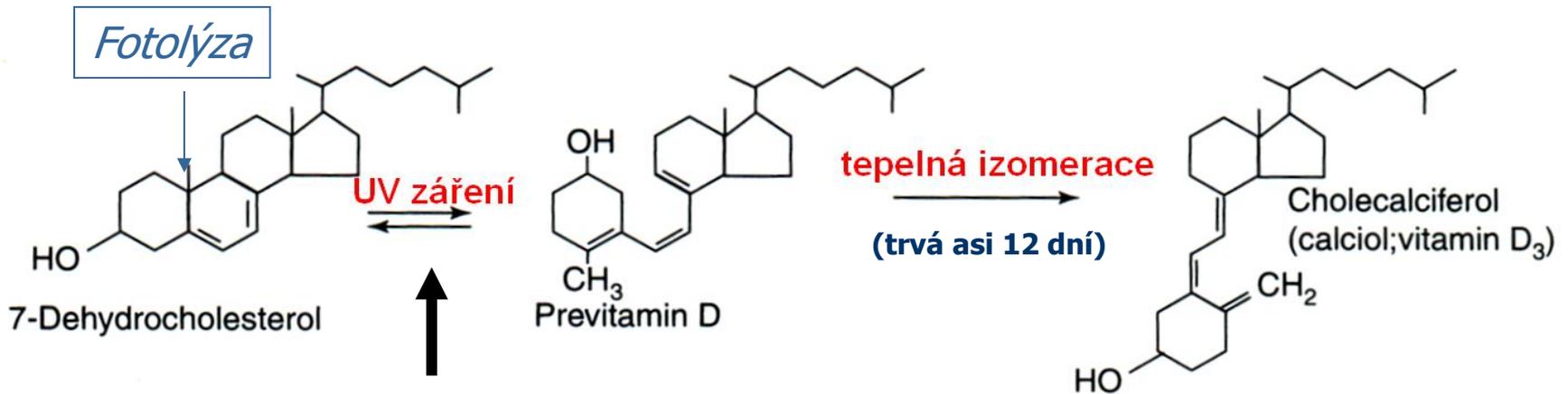
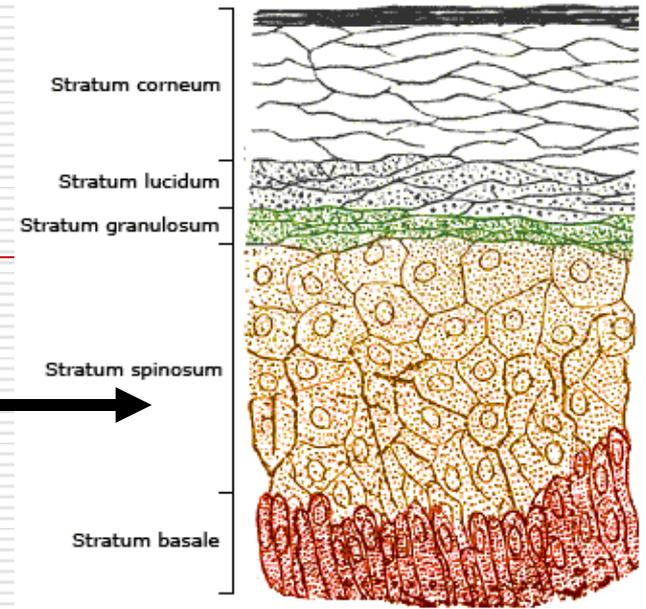
- ✘ Inadequate production of parathyroid hormone - *hypoparathyroidism* - typically results in decreased concentrations of calcium and increased concentrations of phosphorus in blood.
 - ✘ Common causes of this disorder include surgical removal of the parathyroid glands and disease processes that lead to destruction of parathyroid glands. The resulting hypocalcemia often leads to tetany and convulsions, and can be acutely life-threatening. Treatment focuses on restoring normal blood calcium concentrations by calcium infusions, oral calcium supplements and vitamin D therapy.
-

Vitamin D (Calcitriol)

- ❑ Bioactive vitamin D or calcitriol is a steroid hormone that has long been known for its important role in regulating body levels of calcium and phosphorus, and in mineralization of bone.
 - ❑ This hormone has biologic effects which extend far beyond control of mineral metabolism.
-

Vitamin D- synthesis

UV radiation 270 – 300 nm

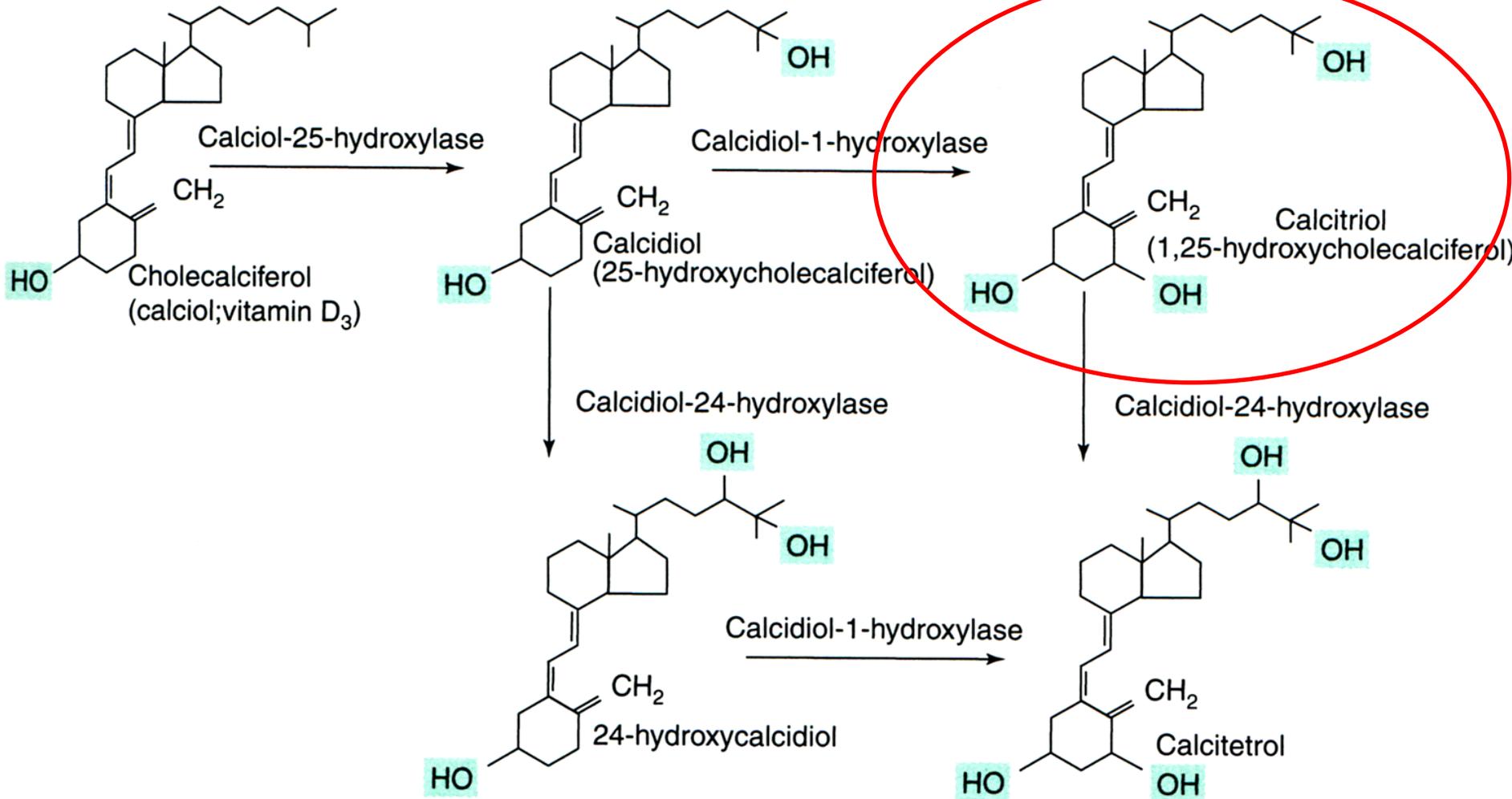


Non-enzymatic reaction in the skin

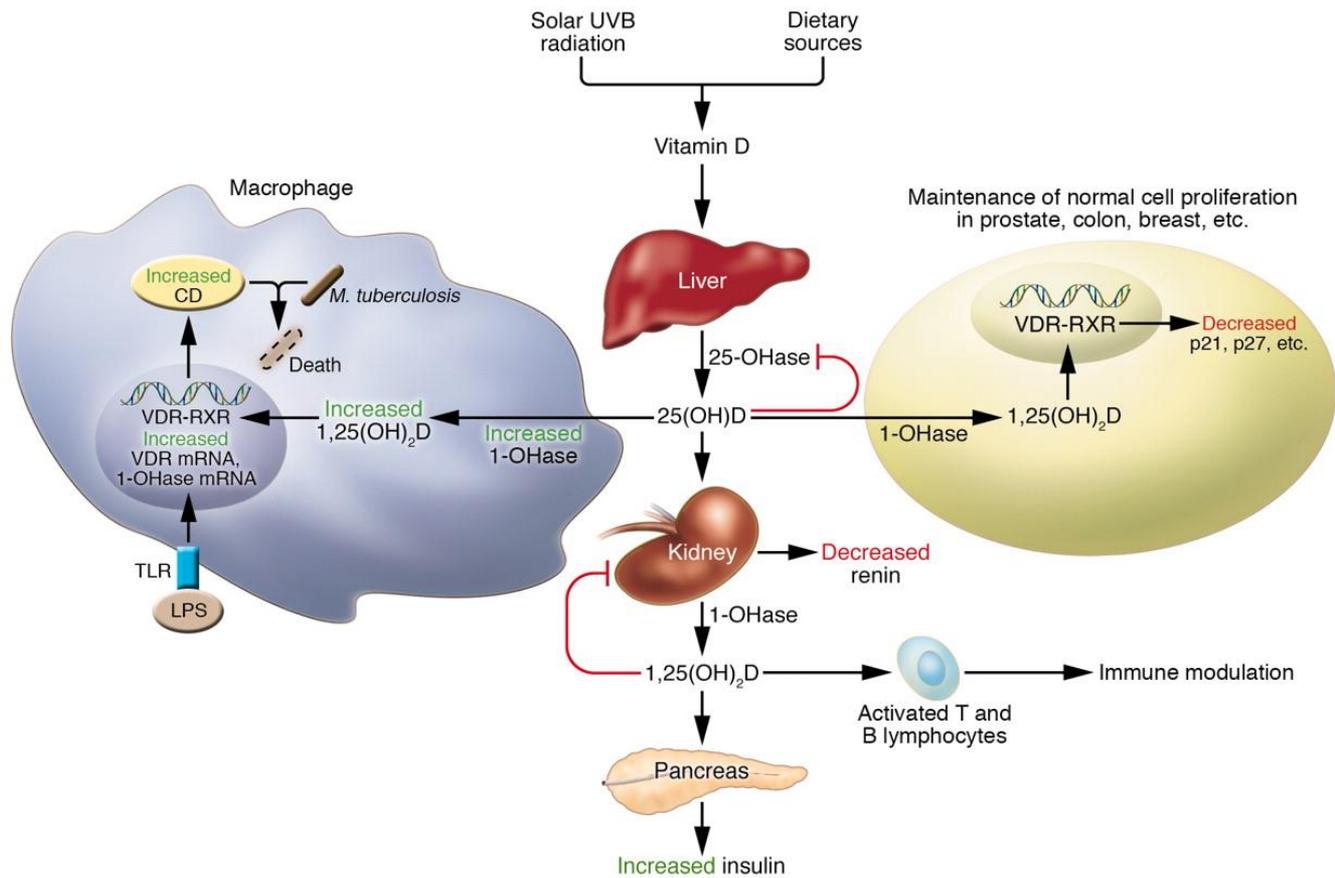
Transport to liver

Liver

Kidneys



Inactive form



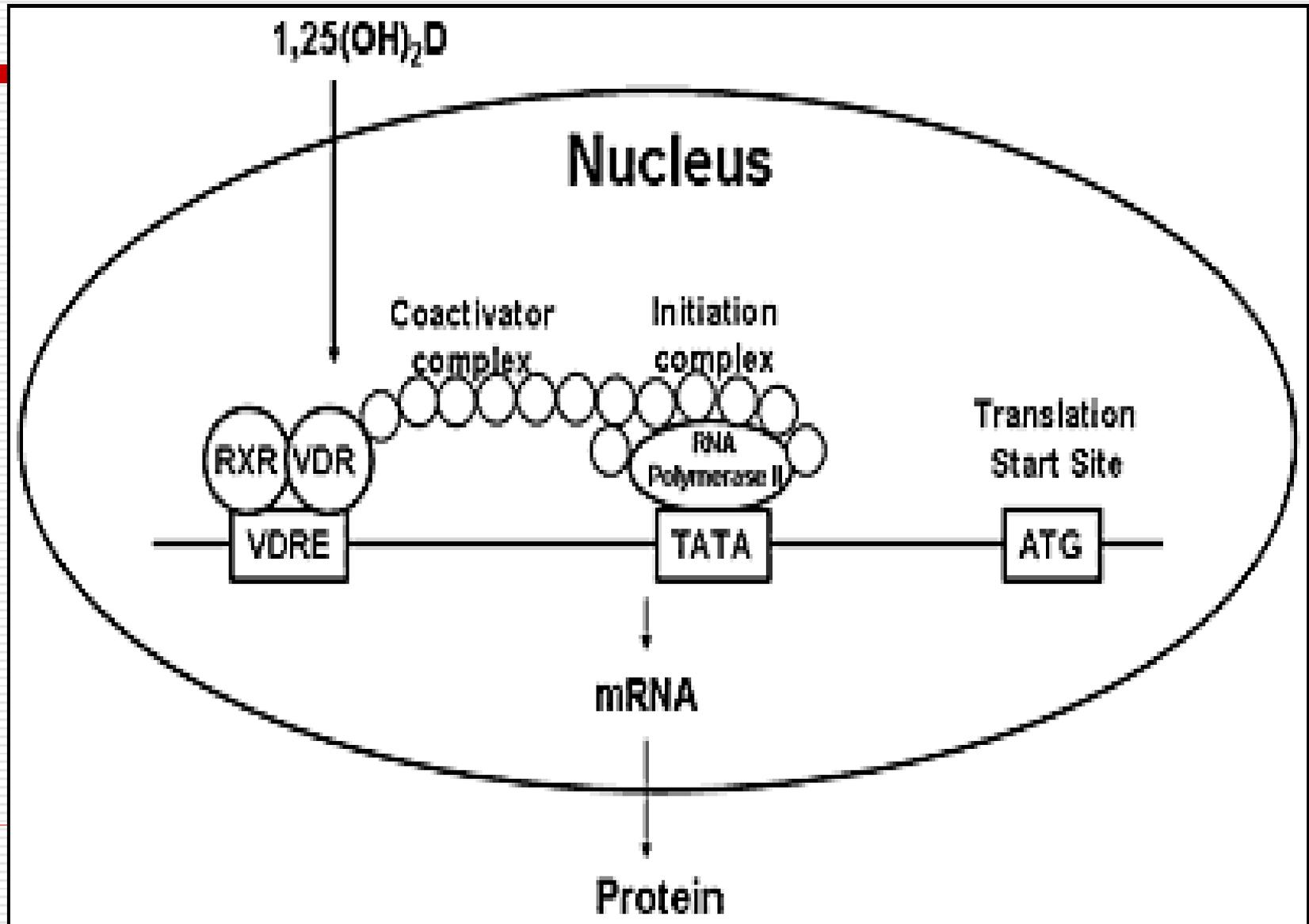
Holick, M. F. J. Clin. Invest. 2006;116:2062-2072



Vitamin D Receptor Binding and Interactions with DNA

- Being lipids, steroid hormones enter the cell by simple diffusion across the plasma membrane. The receptors exist either in the cytoplasm or nucleus, which is where they meet the hormone. When hormone binds to receptor, a characteristic series of events occurs:
 - *Receptor activation* is the term used to describe conformational changes in the receptor induced by binding hormone. The major consequence of activation is that the receptor becomes competent to bind DNA.
-

Vitamin D at the level of DNA

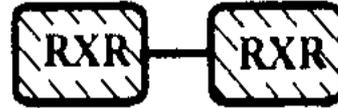


Vitamin D Receptor Binding and Interactions with DNA

- *Activated receptors bind to "hormone response elements", which are short specific sequences of DNA which are located in promoters of hormone-responsive genes. In most cases, hormone-receptor complexes bind DNA in pairs, as shown in the figure below.*
 - *Transcription from those genes to which the receptor is bound is affected. Most commonly, receptor binding stimulates or inhibits transcription of different genes. The hormone-receptor complex thus functions as a transcription factor.*
-

Nuclear receptor function

Receptor dimer



Activator

9-cis RA



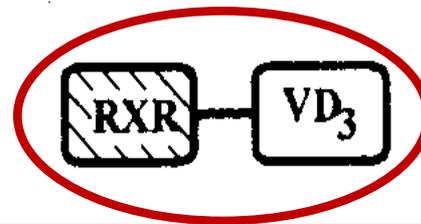
(ATRA, 9-cis RA)



peroxisome proliferators

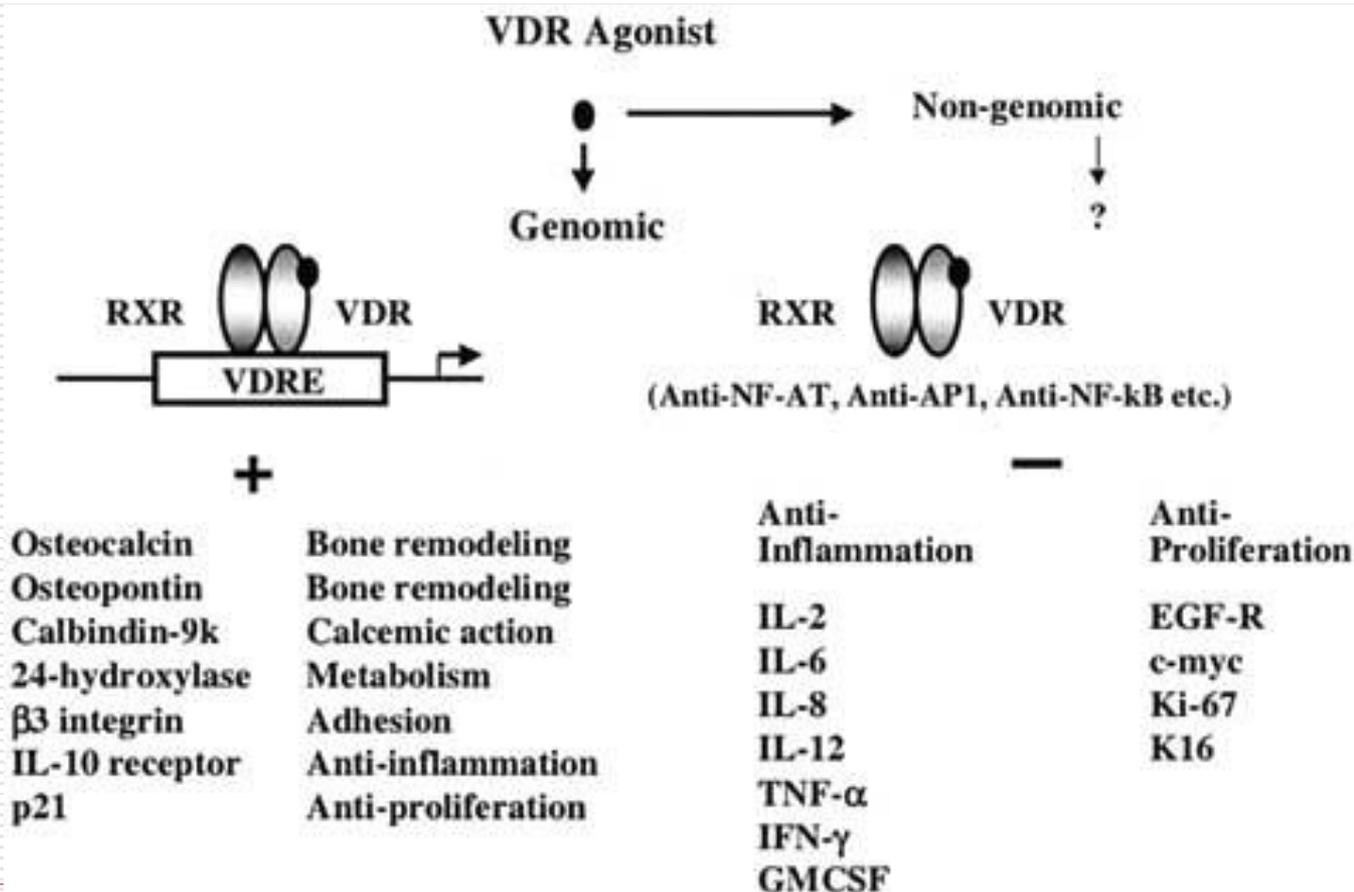


T₃



VD₃

Regulation of gene expression by VDR



The vitamin D receptor and mechanism of action

- The vitamin D receptor forms a complex with another intracellular receptor, the retinoid-X receptor, and that heterodimer is what binds to DNA. In most cases studied, the effect is to activate transcription, but situations are also known in which vitamin D suppresses transcription.
 - The vitamin D receptor binds several forms of cholecalciferol. Its affinity for 1,25-dihydroxycholecalciferol is roughly 1000 times that for 25-hydroxycholecalciferol, which explains their relative biological potencies.
-

Vitamin D deficiency

- ❑ The classical manifestations of vitamin D deficiency are **rickets**, which are seen **in children** and results in bony deformabilities including bowed long bones.
 - ❑ Deficiency **in adults** leads to the **osteomalacia**. Both rickets and osteomalacia reflect impaired formation of newly synthesized bone matrix, and usually result from a combination of inadequate exposure to sunlight and decreased dietary intake of vitamin D.
 - ❑ Vitamin D deficiency or insufficiency occurs in several other situations, which you might predict based on the synthetic pathway described above:
 - ❑ *Genetic defects in the vitamin D receptor*: a number of different mutations have been identified in humans that lead to **hereditary vitamin D resistance**.
 - ❑ Severe **skin, liver or kidney disease**: this can interfere with generation of the biologically active form of vitamin D.
 - ❑ **Insufficient exposure to sunlight**: Elderly people that stay inside and have poor diets often have at least subclinical deficiency.
-

Osteomalacia and rickets

- Classically, the deficiency of vitamin D, essential for the absorption of calcium, has been the major cause of rickets in the child and osteomalacia in the adult resulting in absence or delay in the mineralization of growth cartilage or newly formed bone collagen.
-

Osteomalacia and rickets

- ❑ As a consequence of a low serum phosphate and normal serum calcium.
 - ❑ Two such conditions are *x-linked hypophosphatemic rickets/osteomalacia* and *oncogenic osteomalacia*.
 - ❑ When present, the signs of rickets and osteomalacia in the low serum phosphate states are indistinguishable from the classic hypocalcemic states.
-

Differential diagnosis of hypophosphatemic rickets in children

| | VDRR | Proximal RTA | Dent's disease |
|-------------------|------------------|--------------|------------------|
| Gender | Both | Both | Male |
| Ser. phosphate | Low | Low | Low |
| Ser. calcium | Normal | Low | Normal |
| Calcitriol levels | Normal/low | Low | Normal/Mild high |
| Hypercalciuria | No | No | Yes |
| Nephrocalcinosis | No | No | Yes |
| Ser. PTH | Normal/mild high | High | Normal |

VDRR = Vitamin-D resistant rickets; RTA = Renal tubular acidosis;
PTH = Parathormone

Vitamin D deficiency

- ❑ Sunscreens, especially those with SPF ratings greater than 8, effectively block synthesis of vitamin D in the skin.
 - ❑ **Vitamin D toxicity:**
 - ❑ Excessive exposure to sunlight does not lead to overproduction of vitamin D.
 - ❑ Vitamin D toxicity is inevitably the result of overdosing on vitamin D supplements. Ingestion of milligram quantities of vitamin D over periods of weeks or months can be severely toxic to humans and animals.
-

Heritability of vitamin D insufficiency

- 2 GWASy – 3 polymorphic areas
 - 4p12- GC gene(rs2282679)
 - 11q12- DHCR7/NADSYN1 (rs2211q12)-7-dehydrocholesterol reductase/NAD synthetase 1
 - 11p15-CYP2R1 (rs10741657)-cytochrom P450, subfamily IIR
 - 1-4% of the whole variance of serum 25(OH)D3 levels
-

Vitamin D and health

Deficit and insufficiency of vitamin D = **global healthy problem.**

High risk for acute and chronic disease, as

- ❑ Infection diseases
- ❑ Autoimmune diseases
- ❑ DM type I and II
- ❑ High risk of atherosclerosis
- ❑ Some tumor types (colorectal carcinoma, breast and prostate cancer, ovarian cancer)
- ❑ Cognitive dysfunction
- ❑ Infertility
- ❑ Gravidity and around delivery complications

Pludowski P et al. [Vitamin D effects on musculoskeletal health, immunity, autoimmunity, cardiovascular disease, cancer, fertility, pregnancy, dementia and mortality—A review of recent evidence](#), *Autoimmunity Reviews*, Volume 12, Issue 10, August 2013, Pages 976-989

Insufficiency of vitamin D

- ❑ Can be recognised in a half of „healthy“ adults in developed countries.
 - ❑ Vitamin D levels in the winter seem to be too low in latitude more than 35° without supplementation by sunshine and diet
 - ❑ High heritability - to 53% - important influence of gene polymorphisms (SUNLIGHT consortium – Study of Underlying Genetic Determinants of Vitamin D and Highly Related Traits, based 2008)
-

Calcitonin

- ❑ Calcitonin is a hormone known to participate in calcium and phosphorus metabolism. Its main role is to increase calcium deposition in bones.
 - ❑ In mammals, **the major source of calcitonin is from the parafollicular or C cells in the thyroid gland**, but it is also synthesized in a wide variety of other tissues, including the lung and intestinal tract.
 - ❑ Calcitonin is a 32 amino acid peptide cleaved from a larger prohormone. It contains a single disulfide bond, which causes the amino terminus to assume the shape of a ring.
 - ❑ Alternative splicing of the calcitonin pre-mRNA can yield a mRNA encoding calcitonin gene-related peptide; that peptide appears to function in the nervous and vascular systems. The calcitonin receptor has been cloned and shown to be a member of the seven-transmembrane, G protein-coupled receptor family.
-

Control of calcitonin secretion

- ❑ **The most prominent factor controlling calcitonin secretion is the extracellular concentration of ionized calcium.**
 - ❑ Elevated blood calcium levels strongly stimulate calcitonin secretion, and secretion is suppressed when calcium concentration falls below normal.
 - ❑ A number of other hormones have been shown to stimulate calcitonin release in certain situations, and nervous controls also have been demonstrated.
-

Cytokines, prostaglandins, NO, and leukotrienes

- There is evidence that polymorphisms of IL-1, IL-6, TNF- α , and their receptors can influence bone mass in humans.
 - Prostaglandins have both stimulatory and inhibitory actions; the predominant effect of PGE₂, which is the major prostaglandin produced by bone cells, is to stimulate both resorption and formation.
 - Prostaglandins, particularly PGE₂, are produced by bone cells largely through the action of inducible cyclooxygenase 2 (COX₂). COX₂ is induced by most of the factors that stimulate bone resorption and thus may enhance the response to these agents. Treatment with COX inhibitors blunts the response to impact loading and fluid shear stress, indicating that prostaglandins play an important role in the response on mechanical forces, and this may be enhanced by estrogen. In epidemiologic studies, small increases in BMD and decreases in fracture risk have been reported in individuals using NSAIDs.
-

Cytokines, prostaglandins, NO, and leukotrienes

- NO is produced by bone cells and is a cofactor for the anabolic response to mechanical loading. However, unlike prostaglandins, NO may inhibit bone resorption, perhaps by increasing OPG production.
 - Leukotrienes, the products of lipoxygenase, can affect bone by stimulating resorption and inhibiting formation.
-

Bone System

Immune System

Vascular System

RANK
RANKL
OPG

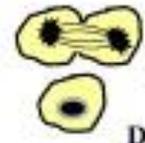
Endothelial and smooth muscle cells
Blood vessels

Osteoblastic Stromal Cells

Dendritic Cells

T Cell

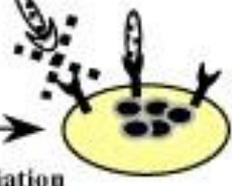
B Cell



Differentiation



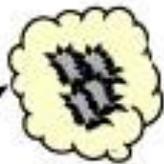
Differentiation



Quiescent Osteoclast



Active Osteoclast



Osteoclast apoptosis



Osteoclast Survival and activation

Proliferation of Hematopoietic Stem Cell (CFU-GM)

Fusion of Osteoclastic Precursor

Quiescent Osteoclast

Active Osteoclast

Osteoclast Survival and activation

M-CSF

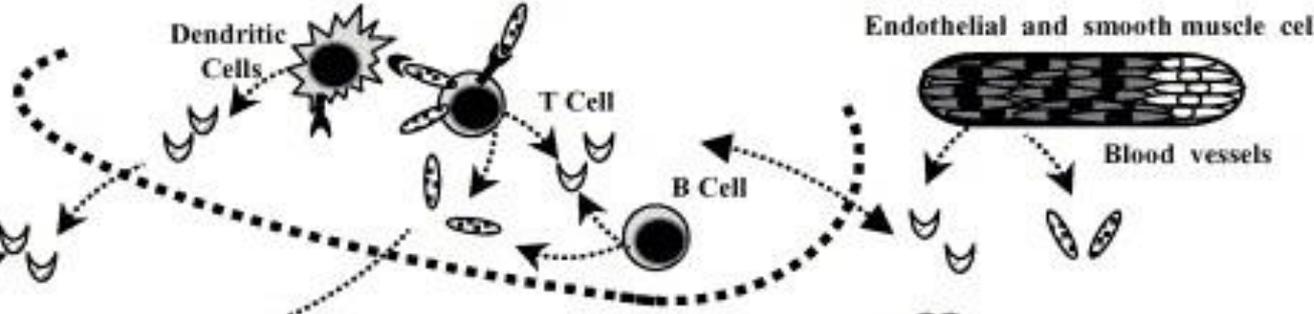
M-CSF
TNF α
IL1

TNF α
IL1

TNF α
IL1

OPG > RANKL

RANKL > OPG



Collagen abnormalities

- A polymorphism of the first intron of the gene coding for the type I collagen $\alpha 1$ chain and increased levels of homocysteine can influence fracture risk independent of BMD (bone mass density). This may be due to differences in helix formation or cross-linking of collagen, challenging the concept that mineral and matrix composition are normal in osteoporosis and that only structural abnormalities account for skeletal fragility.
-

| Gene | Mutation | Disease |
|-------------|--|--------------------------------------|
| RANK | 18 bp duplication | Familial expansile osteolysis |
| | 27 bp duplication | Early onset Paget's disease |
| | 15 bp duplication | Expansile skeletal hyperphosphatasia |
| RANKL | Deletion of amino acids 145-177 | Autosomal recessive osteopetrosis |
| | A single nucleotide change (596T-A) in exon 8 of both alleles | Autosomal recessive osteopetrosis |
| | Deletion of two nucleotides (828_829delCG) | Autosomal recessive osteopetrosis |
| OPG | Deletion making OPG inactive | Juvenile Paget's disease |
| | 20 bp deletion resulting in premature termination of OPG translation | Juvenile Paget's disease |

STROMAL CELLS
(NORMAL)



$\frac{\text{RANKL}}{\text{OPG}}$

STROMAL CELLS
(GIANT CELL TUMOR)



$\frac{\text{RANKL}}{\text{OPG}}$

MULTIPLE MYELOMA



$\xrightarrow{\text{PTHrP}}$

$\frac{\text{RANKL}}{\text{OPG}}$

BREAST CANCER



$\xrightarrow{\text{PTHrP}}$

$\frac{\text{RANKL}}{\text{OPG}}$

PROSTATE CANCER



$\frac{\text{RANKL}}{\text{OPG}}$

X-linked hypophosphatemic osteomalacia

- ❑ The condition is characterized by low tubular reabsorption of phosphate in the absence of secondary hyperparathyroidism.
 - ❑ X-linked hypophosphatemia occurs in about 1 in 25,000 and is considered the most common form of genetically induced rickets.
-

Oncogenic osteomalacia

- Oncogenic osteomalacia is a paraneoplastic syndrome in which a bone or soft tissue tumor or tumor-like lesion induces hypophosphatemia and low vitamin D levels that reverse when the inciting lesion is resected.
-

Oncogenic osteomalacia

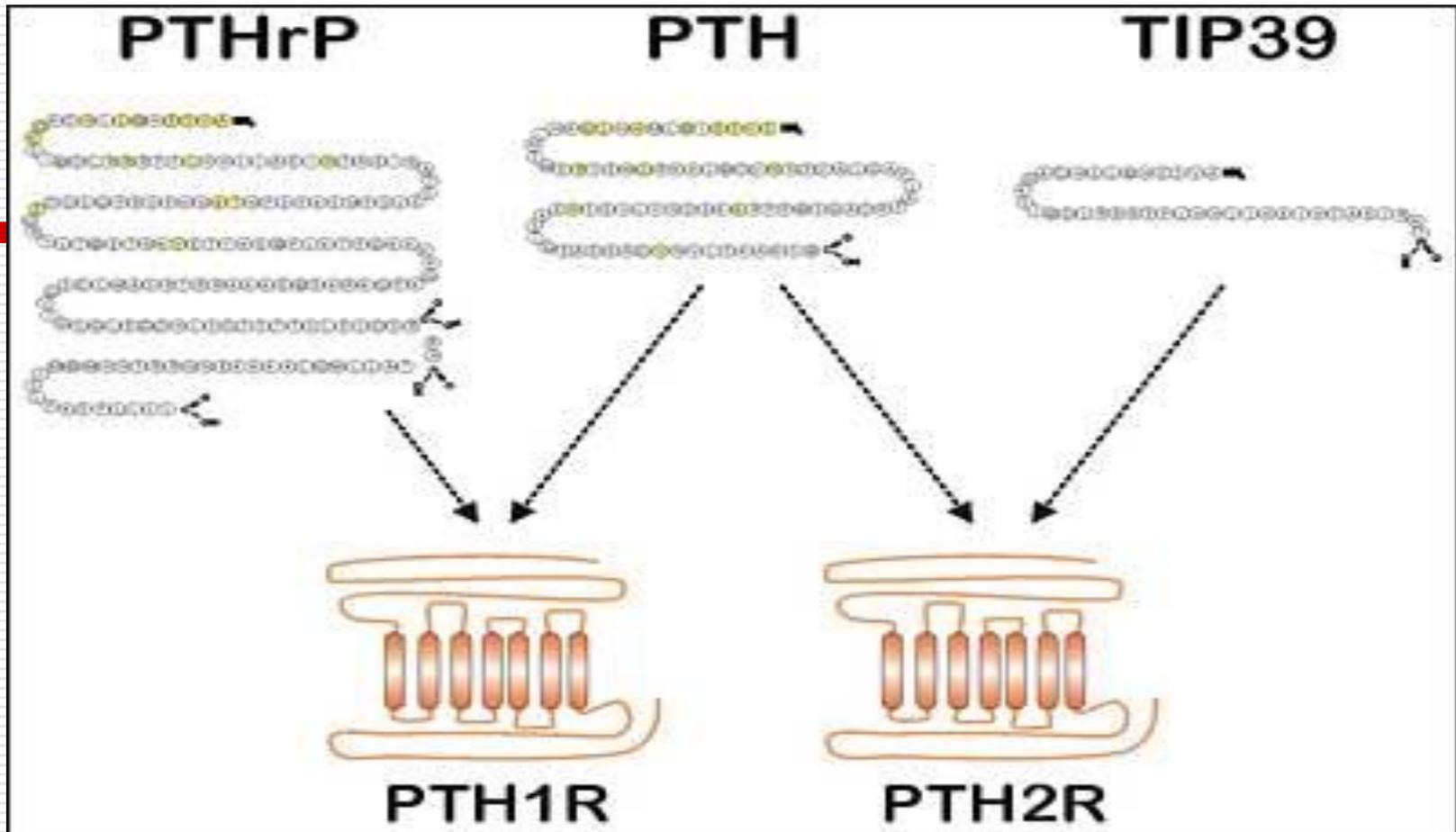
- In the past 15 or so years, a humoral factor, **phosphatonin**, has been identified in clinical and experimental studies as being responsible for the serum biochemical changes.
 - Phosphatonin causes hyperphosphaturia by inhibiting the reabsorption of phosphate by the proximal renal tubules.
 - Fibroblast growth factor 23, phosphate-regulating gene with homologies to endopeptides located on the 'x' chromosome (PHEX) and matrix extracellular phosphoglycoprotein (MEPE) are candidates proposed for the production of phosphatonin and the altered pathophysiology in oncogenic osteomalacia.
-

Oncogenic osteomalacia or tumor-induced osteomalacia (TIO)

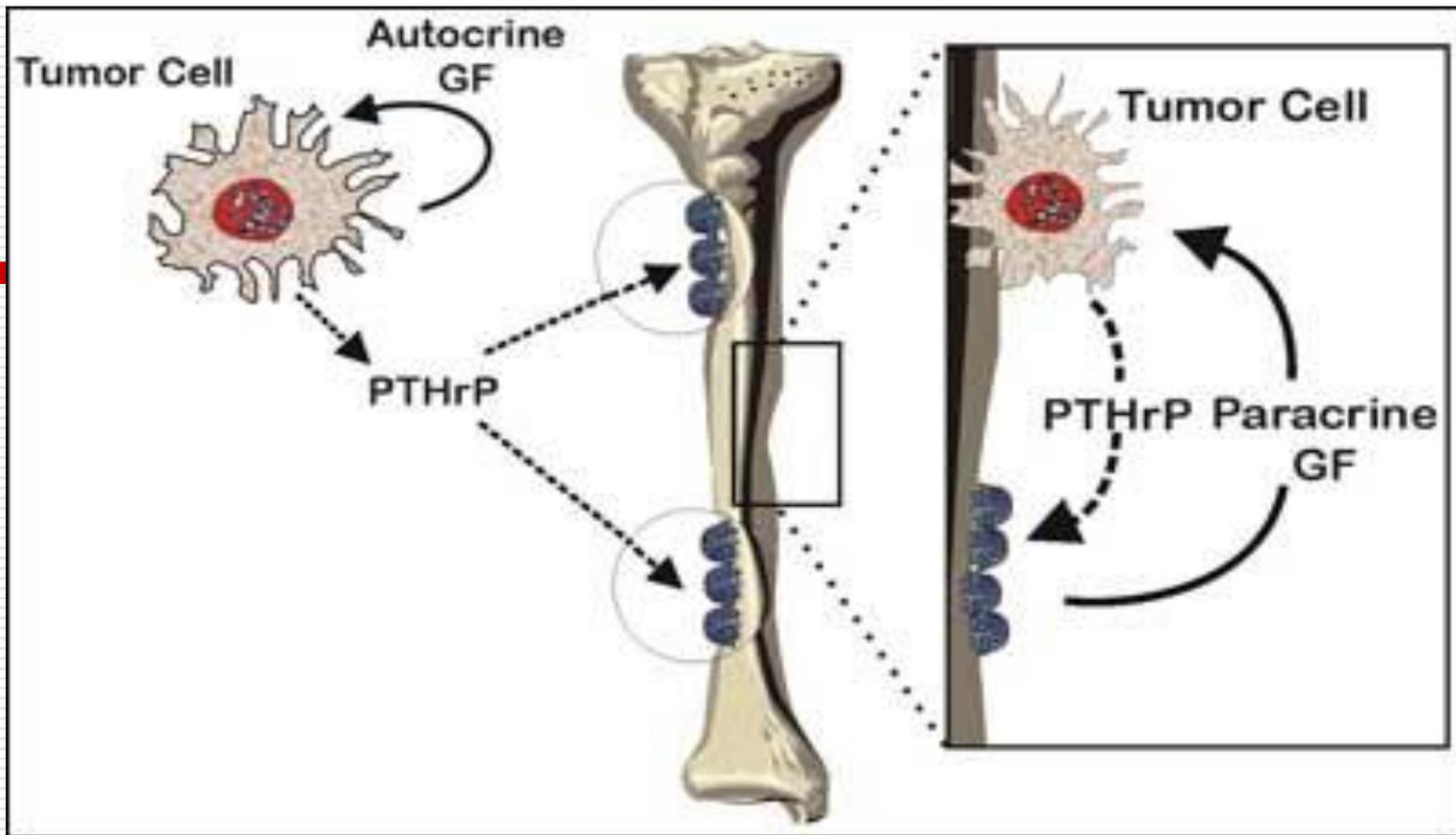
- ❑ To date, more than 160 cases have been reported. Due to this relative rarity, its diagnosis is usually delayed by months or years.
 - ❑ TIO combines severe hypophosphatemia, hyperphosphaturia, very low plasma $1,25\text{-(OH)}_2$ vitamin D levels and severe osteomalacia.
-

Parathyroid Hormone Relation Peptide (PTHrP)

- ❑ PTHrP was discovered as mediator of syndrome "**humoral hypercalcemia of malignancy**" (**HHM**).
 - ❑ During the syndrome in different type of cancer (in absence of metastases) similar compounds to PTH are produced which is related to:
 - ❑ **Hypercalcemia**
 - ❑ **Hypophosphatemia**
 - ❑ **Increased cAMP excretion by urine**
 - ❑ The effects are similar to those caused by PTH; no PTH levels are detected.
-



Genetic families of PTH and PTHrP: PTHrP, PTH and TIP39 are probably members of the same genetic family. Their receptors PTH1R and PTH2R are 7 transmembrane G protein-coupled receptors.



Production of PTHrP regulated by growth factor (GF) in tumor states. Tumor cells are able to be stimulated at a distance (outside the bone) by autocrine growth factors to an increased production of PTHrP. It reaches via circulation the bone tissue and supports bone resorption. Metastatic tumor cells in the bone are able to secrete PTHrP supporting bone resorption and paracrine growth factors which further support PTHrP production.

Děkuji za pozornost

