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VKP 2018

20. 4. 2018

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THE SYSTEMIC inflammatory response syndrome (SIRS)

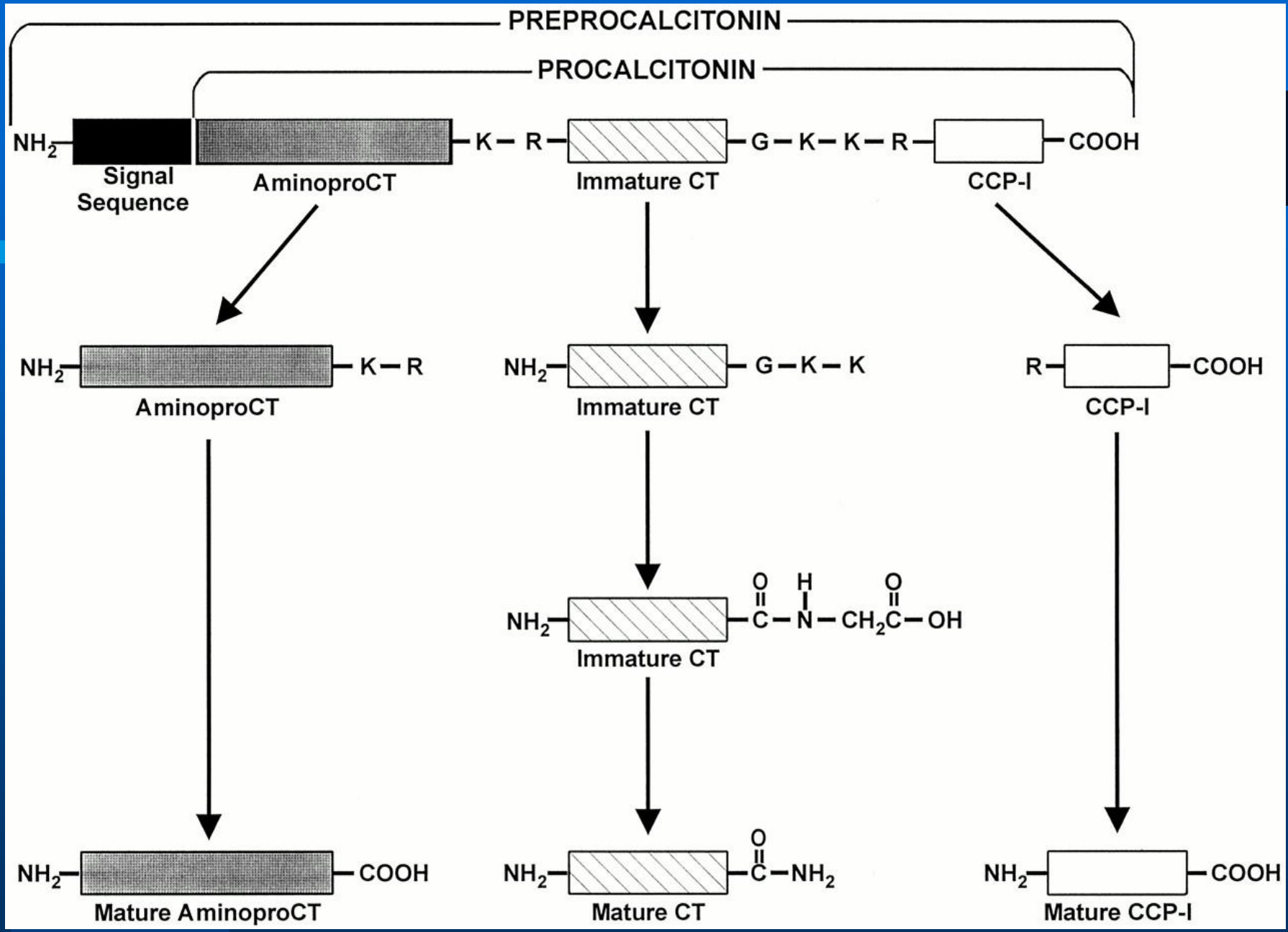
- a clinical expression of nonspecific inflammation, is a major cause of morbidity and mortality and is a leading cause of death in intensive care units.
- SIRS can be initiated by a variety of causes, including infection, and may vary in severity from mild to life threatening.
- Few reliable serum markers exist that can provide useful clinical information regarding the severity of illness or the prognosis for the many SIRS-related conditions.

Sérový pre-CT jako klinický marker sepse

- Serum pre-CT is a clinically important serum marker for systemic inflammation and sepsis. Maximal levels were consistently elevated, and the highest values were seen in the most severely ill patients or fatalities. The elevated serum pre-CT not only identifies patients with these conditions, but also reflects their clinical course. To be most useful for prognosis, daily determinations should be made, because it is the peak value that is the most informative.

Posttranslational processing of CT precursors

- Mature CT is produced in the form of a preprohormone that undergoes extensive posttranslational processing. Initially, the signal sequence is cleaved, producing pro-CT. The molecular moieties that exist at low levels in the peripheral circulation of normal persons are pro-CT, aminopro-CT, mature CT, CCP-I, and free conjoined CT:CCP-I. The mature, free CT molecule has 32 amino acids, lacks a glycine at its carboxyl-terminus, and is amidated. This amidation confers much of the biological activity to this hormone. There is also a CCP-II peptide that is present mostly in neural tissue. K, Lysine; G, glycine; R, arginine. Enzymatic cleavage occurs at the basic amino acid pairs or triplets.


PREPROCALCITONIN
PROCALCITONIN
NH2
Signal Sequence
AminoproCT
K – R
Immature CT
G – K – K – R
CCP-I
COOH
NH2
AminoproCT
K – R
NH2
Immature CT
G – K – K
R
CCP-I
COOH
NH2
Immature CT
O
H
O
C – N – CH2C – OH
NH2
Mature AminoproCT
COOH
NH2
Mature CT
O
C – NH2
NH2
Mature CCP-I
COOH

Prokalcitonin (PCT)

- 116 AK , produkován C buňkami štítné žlázy.
- Zvýšené hladiny: hyperkalcémie, glukokortikoidy,
- Preprokalcitonin je v ER štěpen na prokalcitonin , pak katakalcinem na kalcitonin. Všechen produkovaný PCT v C-buňkách je štěpen na kalcitonin.

PCT jako biomarker sepse

- Za fyziologických okolností jsou proto hladiny PCT v krvi stopové.
- Pokud se prokalcitonin octne v krvi, je problém ho odbourat (poločas 25-30 hod oproti kalcitoninu s 4-5min!!!)
- PCT jako modulátor syntézy NO?
- Nejvyšší hladiny u bakteriální sepse
- Korelace s hladinami prozánětlivých cytokinů-protein akutní fáze.
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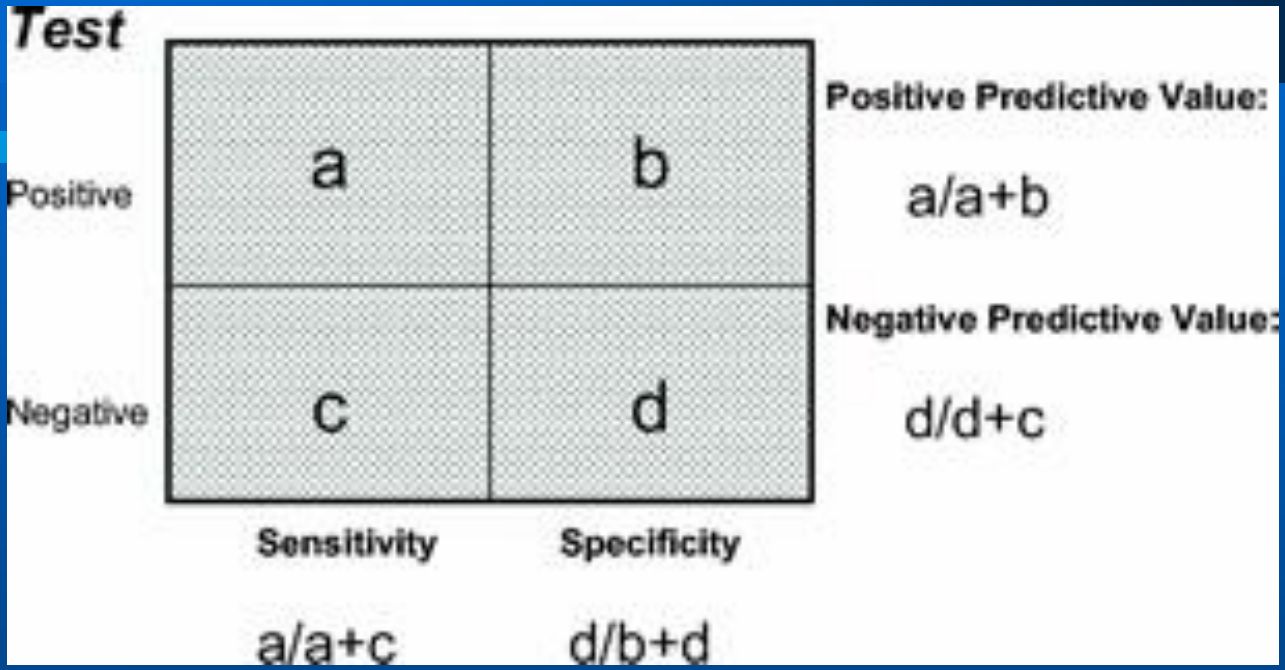
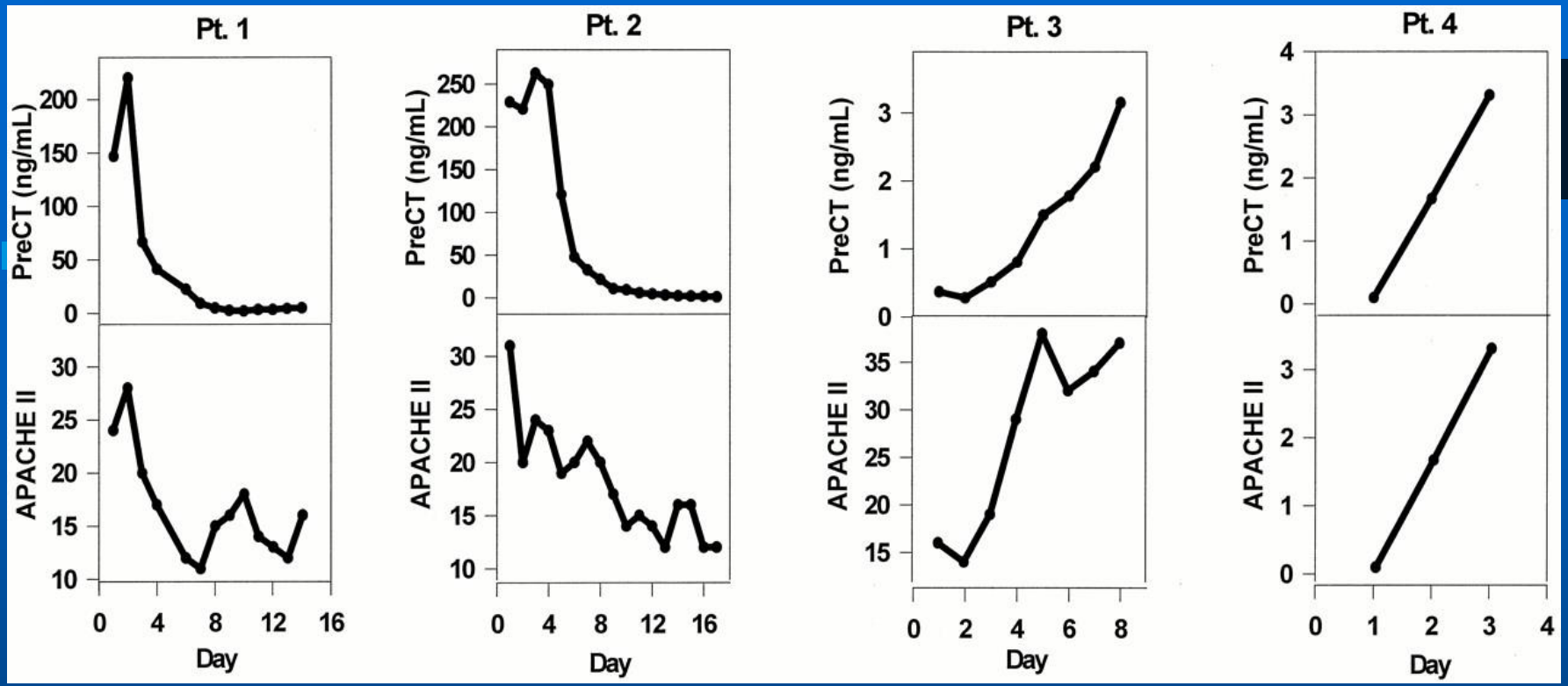


Determination of the sensitivity, specificity, positive predictive value, and negative predictive value of a diagnostic test. The positive likelihood ratio is calculated as the sensitivity/1-specificity, and the negative likelihood ratio as 1-sensitivity/specificity. Positive likelihood ratios over the range of values of the diagnostic test is represented by the receiver operating characteristics curve, the area under the curve being a reflection of the accuracy of the test across a range of values.



Representative time course of pre-CT peptides in systemic inflammation and sepsis. The time-course curves for both serum pre-CT and APACHE II scores followed similar patterns, peaking simultaneously in those select patients who had discrete peaks in their serum levels. The serum levels of pre-CT, determined by the two-site assay in this figure, reflect the daily clinical progress of these patients, indicating improvement or deterioration.

Typ infekce

- Most of the patients had bacterial infections.
- Patients with viral infection commonly, but not always, have considerably lower serum pre-CT values. This probably is related to the lower incidence of associated severe systemic inflammation in viral infection.

Sérové hladiny pre-CT v čase

- The serum pre-CT levels often reflected the patient's daily clinical progress, suggesting improvement or deterioration in select patients who demonstrated discrete peaks in the serum levels. This relationship was based on a close parallelism with the APACHE II score. However, this could not be demonstrated in patients who had only modest elevations of serum pre-CTs without distinguishable peaks.

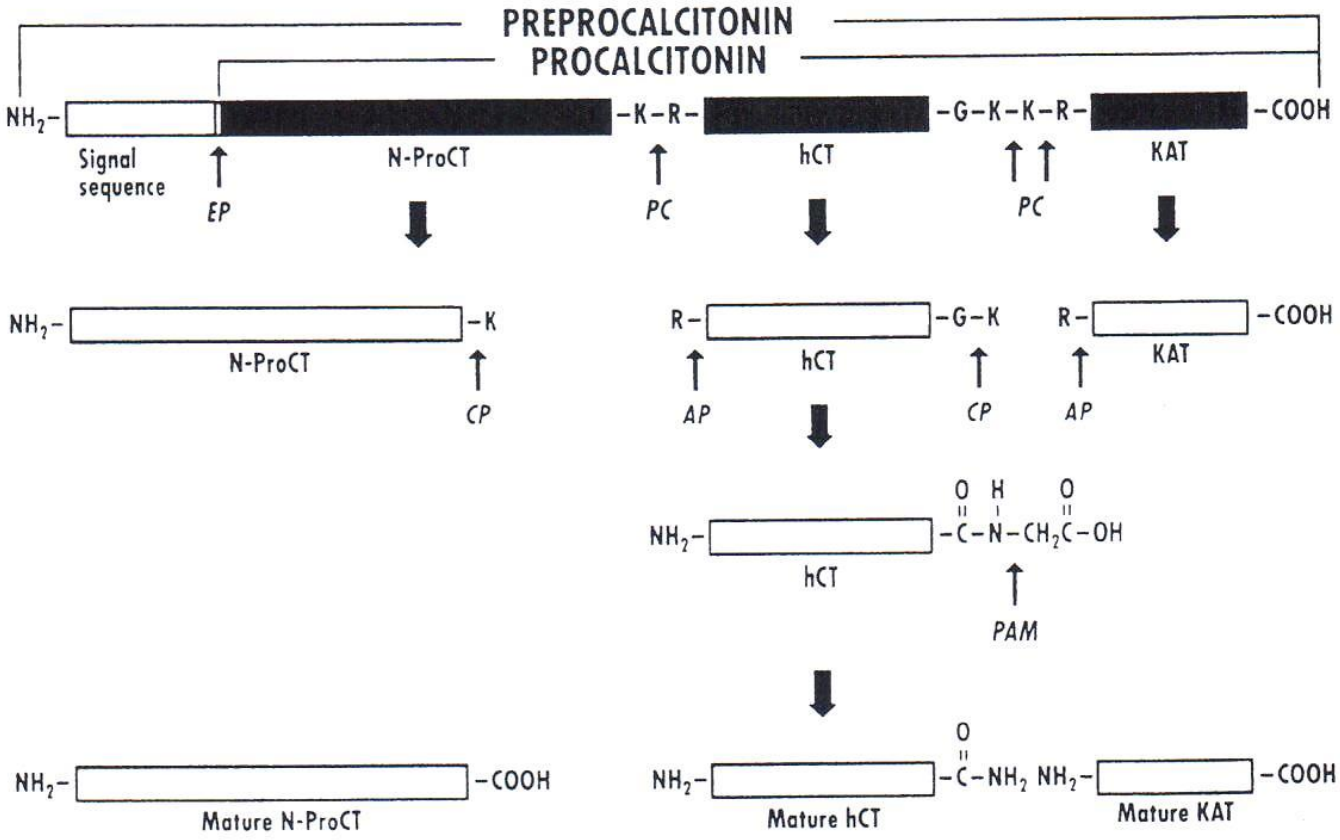


Fig. 1. *Cleavage of procalcitonin (from Meisner 1996). AP = aminopeptidase, CP = carboxypeptidase, CT calcitonin, EP = endopeptidase, KAT = katacalcin, PAM = peptidyl glycine amidating monooxydase, PC prohormone convertase*

Calcitonin gene-related petide (CGRP)

- Rodina -6 členů:
- Kalcitonin, amylin, intermedin (adrenomedulin-2), adrenomedulin a CGRP (α- 37 AK-NS a β-enterické nervy a hypofýza).
- Funkce: modulace NS, KVC, RS, GIT, endokrinního systému, imunitního systému, muskuloskeletálního systému
- Terapie migrény?

Klinický případ 85 letá paní osaměle žijící, po patologické fraktuře kyčle

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Stav kosti u PMP ženy

- Osteoporóza ?
- Osteodystrofie?
- Osteomalácie?
- Kombinace?

Stav kosti u postmenopauzálních žen

- Patologická fraktura
- Bolest (opioidy!)

- Rizikové faktory:
  - Faktory životního stylu
  - Faktory genetické
  - Endokrinopatie

Příčiny osteoporózy

- Nedostatek estrogenů
- Nadbytek glukokortikoidů
- Nedostatek vitaminu K2
- Nedostatečná pohybová aktivita

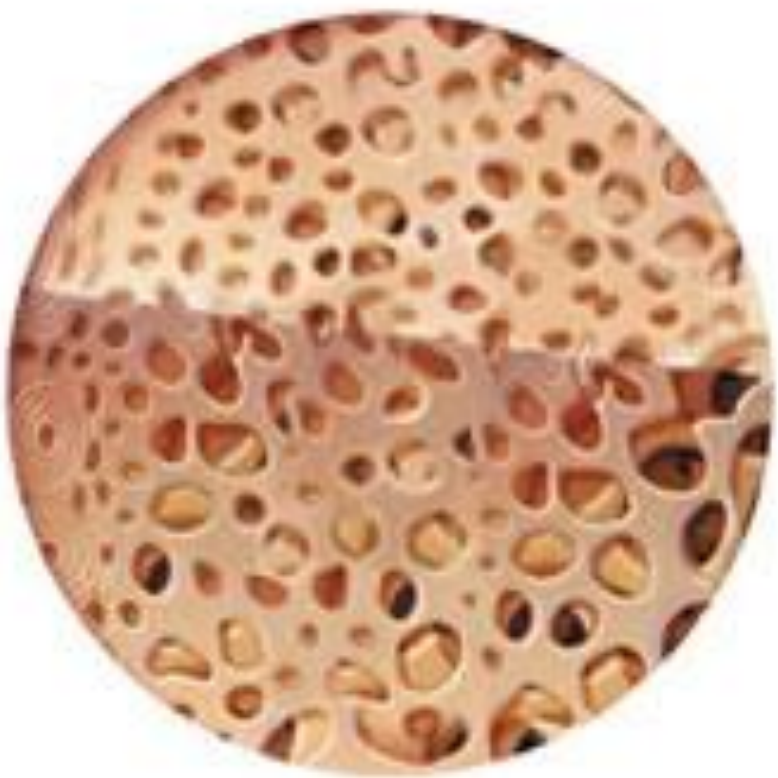
Faktory životního stylu se zvýšeným rizikem fraktur u PMP žen

- Vyšší spotřeba alkoholu
- Léčba některými antacidy
- Vysoká spotřeba kávy
- Anamnéza dlouhodobé imobilizace
- Nízký BMI
- Nízké hladiny kalcia a deficit vitaminu D (nedostatek slunečního záření, chronické renální selhání)

Table 1 Remaining lifetime probability of a major fracture at the age of 50 and 80 years in men and women from Sweden [10] (with kind permission from Springer Science and Business Media)

Site	At 50 years		At 80 years	
	Men	Women	Men	Women
Forearm	4.6	20.8	1.6	8.9
Hip	10.7	22.9	9.1	19.3
Spine	8.3	15.1	4.7	8.7
Humerus	4.1	12.9	2.5	7.7
Any of these	22.4	46.4	15.3	31.7

Osteoporóza



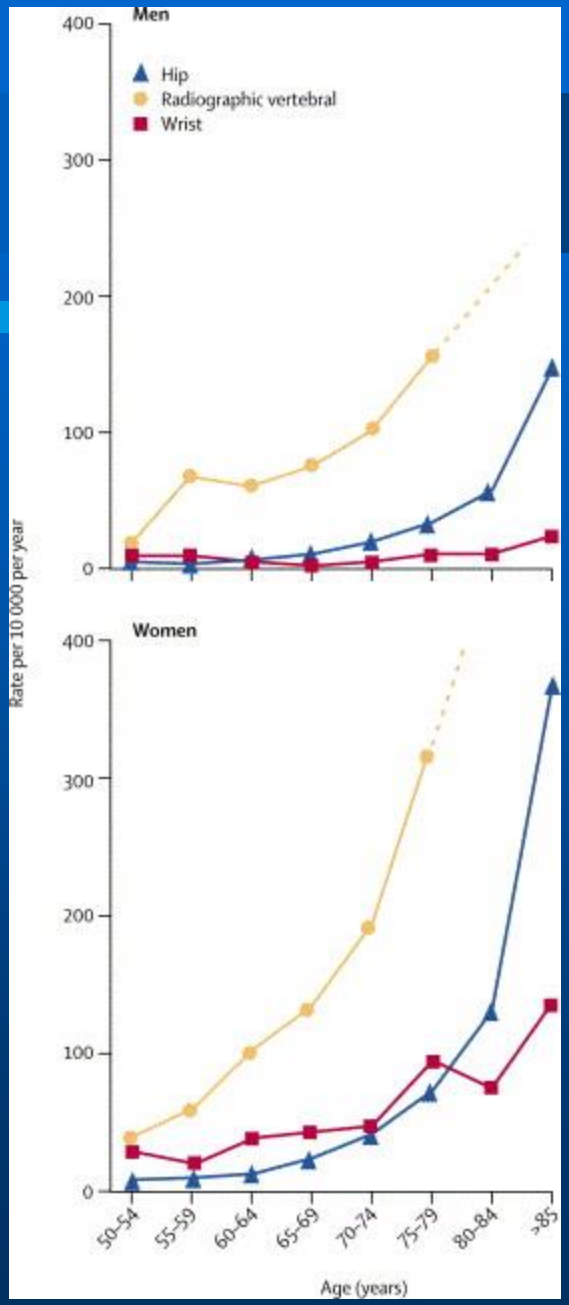
Normal

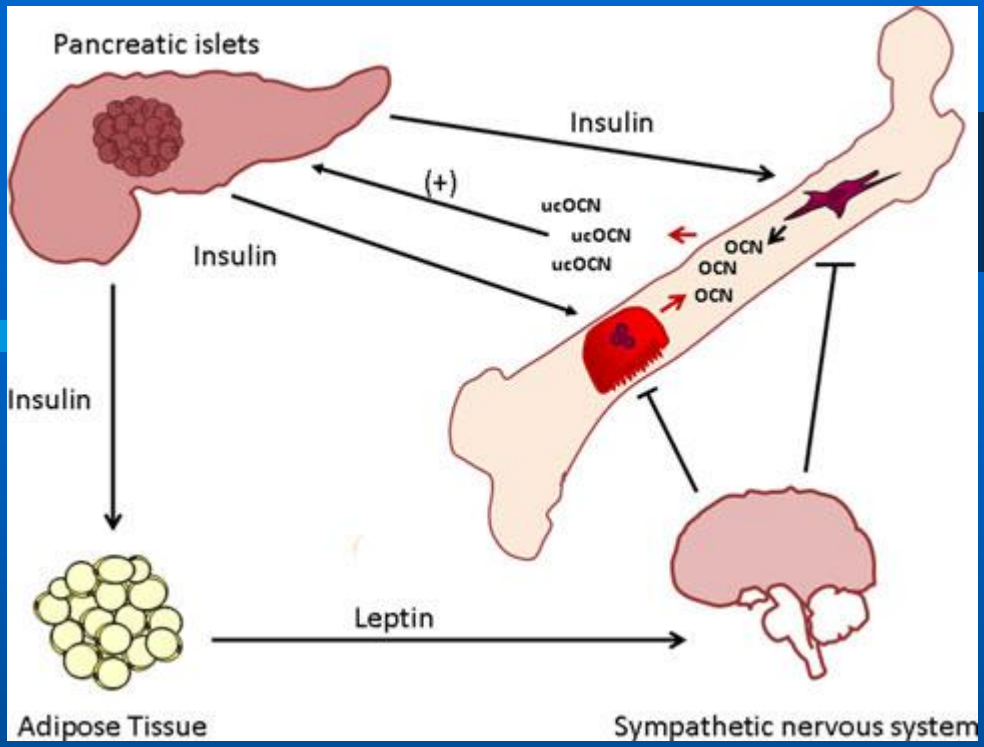
Osteoporotic bone

Etiopatogeneza: chronicky zvýšený podíl mezi osteoklastickou a osteoblastickou aktivitou v kosti

Incidence radiologických fraktur páteře, kyčle a distálního předloktí v závislosti na věku a pohlaví.

Data derived from European Prospective Osteoporosis Study and General Practice Research Database.



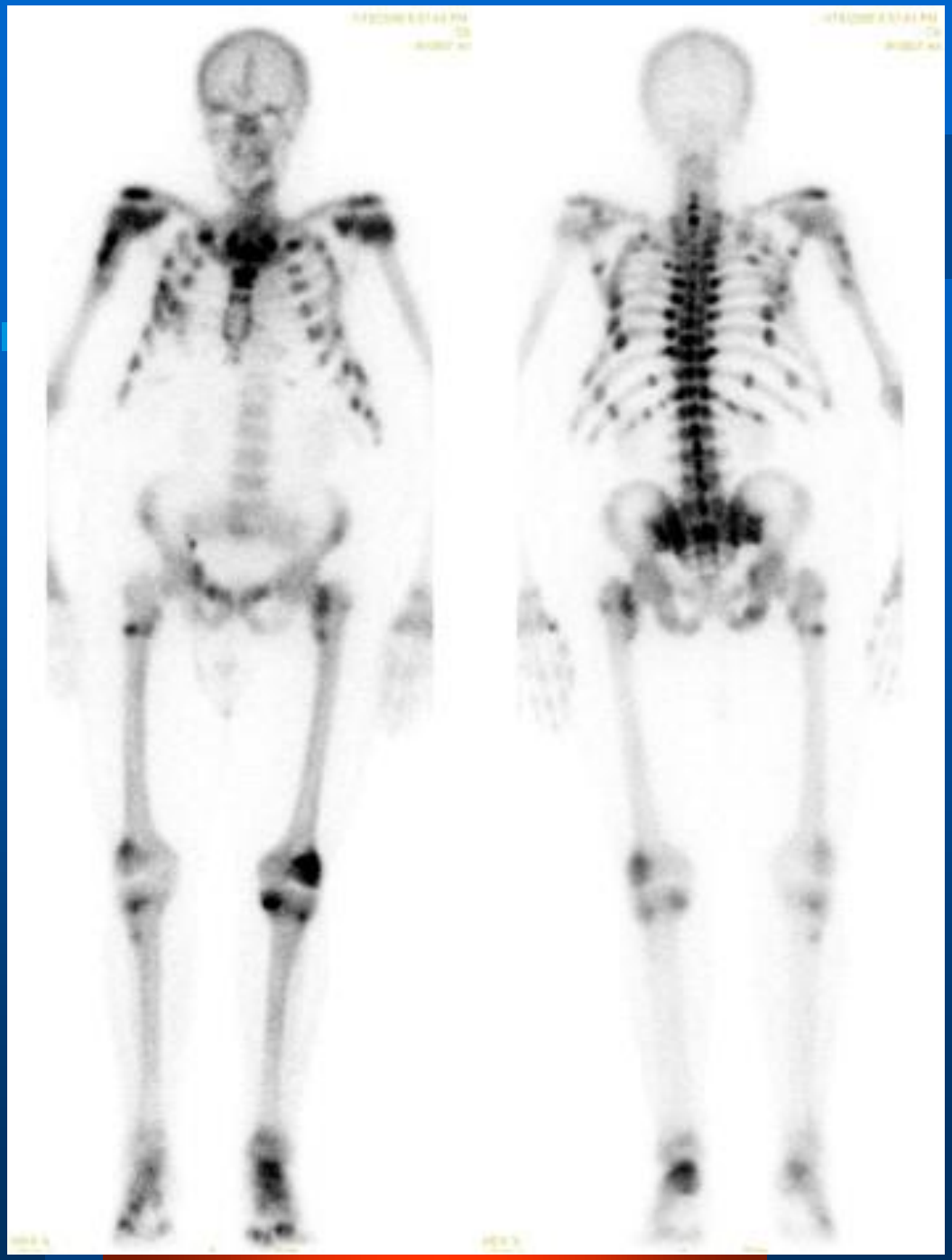


Glukokortikoidy obecně působí jako antagonisté inzulínu …

Předpokládaná reciproká endokrinní regulace funkcí kosti a tukové tkáně: Karboxylovaný osteoKalcin (OCN) je produkován osteoblasty a je následně vázán na hydroxyapatitový minerál vyzrálé kosti.
Během resorbce kosti řízené osteoklasty se uvolňuje do cirkulace nekarboxylovaný osteokalcin (ucOCN), odkud významně podporuje produkci inzulínu pankreatem. Inzulín zvyšuje expresi OCN osteoblasty a zároveň podporuje jeho dekarboxylaci působenou osteoklasty. Inzulín má také pozitivní vliv na sekreci leptinu adipocyty, což vede k inhibici kostní produkce i resorbce hypotalamickým vlivem leptinu. Produkce ucOCN je tak snížena a dochází k modulaci orexigenních efektů ucOCN na produkci inzulínu pankreatem.

Doporučená léčba osteoporózy

	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



^{99}m-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.

Osteodystrofie

- *Sekundární hyperparathyreoidismus*is – obvykle u chronického onemocnění ledvin s tendencí k rozvíji chronického ledvinného selhání v důsledku neschopnosti ledvin resorbovat kalcium- renální osteodystrofie jako projev excesivní kostní remodelace. .
- Jiné příčiny-obvykle nutriční: deficit kalcia a fosfátů ve stravě, nadbytek fosfátů ve stravě.

Onkogenní osteomalácie nebo tumorem indukovaná osteomalácie (TIO)

- Dosud publikováno jen asi 160 případů. Často poddiagnostikována
- Projevy
- Vážná hypofosfatémie, hyperfosfaturie, velmi nízké hladiny 1,25-$(OH)_2$ D3
- Závažná osteomalácie

Table 13 Routine procedures proposed in the investigation of osteoporosis

Routine
History including the FRAX clinical risk factors
Examination including height and weight
Blood cell count, sedimentation rate, serum calcium, albumin, creatinine, phosphate, alkaline phosphatase and liver transaminases
Lateral radiograph of lumbar and thoracic spine
Bone densitometry (dual energy X-ray absorptiometry at hip and spine)
Other procedures
Lateral imaging DXA for vertebral fracture assessment (VFA)
Markers of bone turnover, when available

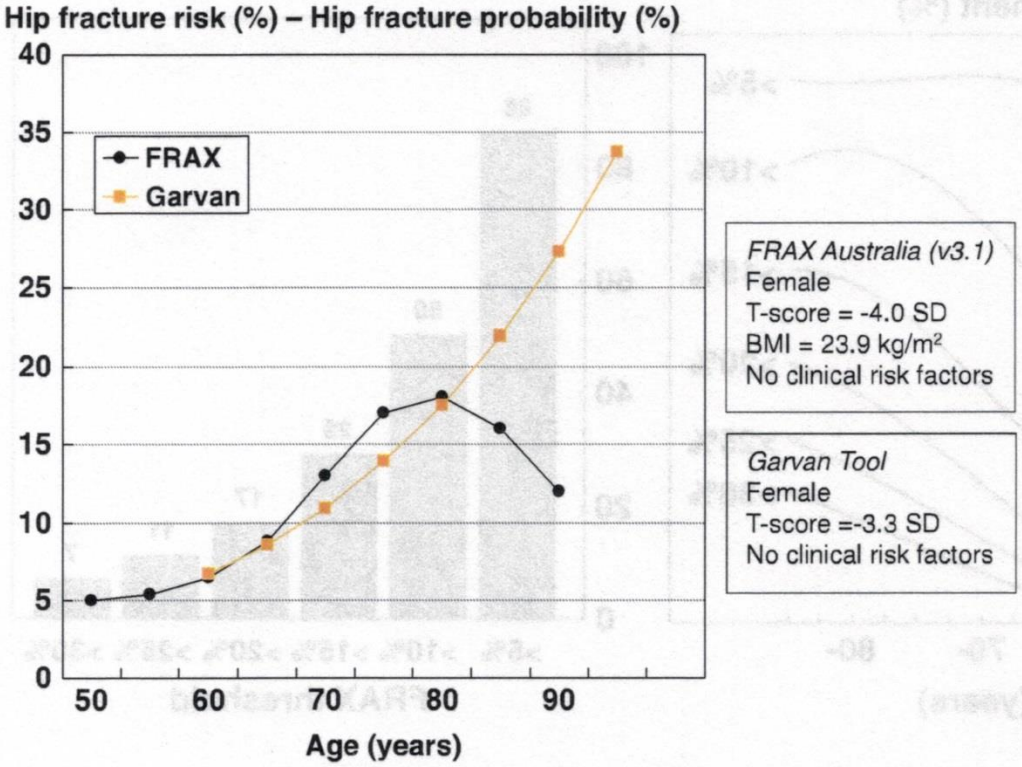


Fig. 10 The risk of hip fracture with age in a model that considers 10-year fracture risk alone (the Garvan tool) and FRAX which computes the probability of hip fracture from the fracture and death hazards (FRAX). The T-scores are set differently in the two models so that the risks are approximately equal at the age of 60 years. Data are computed from the respective websites [127]. With kind permission from Springer Science and Business Media

Table 10 Risk factors associated with falls (adapted from [131] with permission from Elsevier)

1.	Impaired mobility, disability
2.	Impaired gait and balance
3.	Neuromuscular or musculoskeletal disorders
4.	Age
5.	Impaired vision
6.	Neurological, heart disorders
7.	History of falls
8.	Medication
9.	Cognitive impairment

Stav kosti u postmenopauzální ženy

Women with a history of anorexia nervosa, panhypopituitarism, androgen insensitivity or other causes of premature ovarian failure are at an exquisitely increased risk of pathological fractures.

Diabetes, hyperparathyroidism, hyperthyroidism and adrenal gland diseases can also put the woman at an increased risk of pathological bone changes, especially during the perimenopausal period.

Absorption disorders, such as celiac disease, gastric bypass, inflammatory bowel disease, or pancreatic disease are associated with impaired vitamin D absorption and possibly a higher risk of osteomalacia.

Stav kosti u postmenopauzální ženy

U žen po patologické fraktuře je potřeba vynechat:

- Heparin
- Antiepileptika
- Inhibitory aromatázy
- Chemoterapii
- Steroidy
- Litium

Screening for Osteoporosis in Women

- Dual-energy X-ray absorptiometry (DEXA) is the method of choice for assessing the bone mass density in postmenopausal women and in the prediction of the risk of pathological fractures.
- The result of DEXA is usually reported as a T-score that represents the difference between the patient's bone density from the mean of the population's normal bone mass density in standard deviations.

Screening for Osteoporosis in Women

- Normal bone mass density should have a T-score less than 1 SD below the mean.
- Bone mass density between 1 to 2.5 SD indicates osteopenia.
- Osteoporosis is defined as a bone mass density below 2.5 SD below the mean.
- Z-score might be more appropriate for the interpretation of a DEXA study result than a T-score. Z-scores consider the patient's age. A Z-score that is below -2.0 is indicative of clinically significant osteoporosis.
- Note: The measurement of hip bone mass density using DEXA has the strongest correlation and predictive power of pathological fractures.

Stav kosti u postmenopauzální ženy - léčba

Low dose estradiol (0.14mg) as a skin path that doesn't require progesterone for endometrial protection is the method of choice in hormonal replacement therapy for the prevention of osteoporotic fractures.

Weight-bearing and non-weight-bearing exercises, especially of the lower limbs, definitely lower the risk of osteoporotic fractures in postmenopausal women and are recommended. Postmenopausal women should be encouraged to limit their alcohol intake to less than 2 drinks per day and to quit cigarette smoking for women.

Treatment of Osteoporosis in Women

Treatment for osteoporosis should be started in any postmenopausal woman:

- Who is older than 50 years.
- Who sustained a fragility fracture before or who has a DEXA t-score below 2.5.
- When loss of bone mass is associated with an elevated 10-year fracture risk using the FRAX online risk calculator.

Treatment of Osteoporosis in Women

This is especially true when the woman is at an increased risk of osteoporotic fractures due to the presence of multiple risk factors.

Bisphosphonates are the mainstay of the treatment of osteoporosis in postmenopausal women and are very important in the secondary prevention of osteoporotic fractures. They decrease the risk of vertebral and non-vertebral fractures, but do not have any effect on the bone mass density.

Unfortunately, bisphosphonates are associated with a significantly increased risk of gastrointestinal tract side effects such as esophagitis.
Selective estrogen-receptor modulators are very effective in the prevention of vertebral and non-vertebral fractures in osteoporotic women, but not in the prevention of hip fractures. They increase bone mass density which is another added advantage over bisphosphonates. Unfortunately, they are associated with an increased risk of venous thromboembolism disease.

Treatment of Osteoporosis in Women

Hormone replacement therapy is known to lower the risk of osteoporosis, especially in women with premature ovarian failure and the risk of osteoporotic-related fractures. They decrease the rate of bone mass density loss and are effective in lowering the rates of hip, vertebral and non-vertebral fractures in postmenopausal women.

They also ameliorate the vasomotor symptoms, urogenital symptoms and mood symptoms of menopause. Hormone replacement therapy use after more than 10 years of menopause is not recommended due to the increased risk of cardiovascular disease.

Parathyroid hormone and calcitonin can be also used for the secondary prevention of osteoporotic fractures in postmenopausal women. Their efficacy is inferior compared to the previous interventions, but they can be used as adjunctive therapy.

Treatment of Osteoporosis in Women

Denosumab was recently approved for the prevention of osteoporotic-related fractures and the treatment of osteoporosis. It reduces the risk of vertebral and non-vertebral fractures in addition to lowering the risk of hip fractures. Denosumab also increases the bone mass density at the lumbar spine and hip.

The main side effects of denosumab are gastrointestinal irritation, dermatitis, limb and back pain, headache and hypercholesterolemia. Because bisphosphonates are very efficacious and considerably cheaper than this option, they remain the first-line therapy for osteoporosis in postmenopausal women. Denosumab has the advantage of being administered only once every six months, but the cost-effectiveness of the drug and the similar efficacy to bisphosphonates makes it a second-line therapy that should be used only in very high-risk patients.

Denosumab

- Denosumab je nový biologický lék určený k léčbě stavů charakterizovaných patologicky zvýšenou kostní resorpcí s následnou ztrátou kostní hmoty a zvýšeným rizikem vzniku fraktur. V současné době je v České republice registrován pro terapii postmenopauzální osteoporózy a pro léčbu úbytku kostní hmoty v souvislosti s androgen deprivační terapií u mužů s nemetastazujícím karcinomem prostaty. Denosumab je unikátní svým složením i cíleným mechanismem účinku. Jde o plně humánní monoklonální protilátku proti cytokinu RANKL (ligand pro receptor aktivátoru nukleárního faktoru kB). RANKL je klíčovým faktorem potřebným k diferenciaci a aktivaci nových generací osteoklastů.

Denosumab

Denosumab se v místech, kde je kost metabolicky aktivní, váže na RANKL a jeho blokádou inhibuje osteoklastogenezi. Ve škále antiporotických léčiv je denosumab řazen mezi inhibitory kostní resorpce. U nemocných léčených denosumabem byl ve srovnání s placebem prokázán významný pokles rizika vzniku osteoporotických fraktur všech typů (vertebrálních i nevertebrálních včetně zlomenin kyčle). Pacienti v klinických hodnoceních léčbu denosumabem dobře tolerovali. Režim podávání v jednorázové subkutánní injekci jednou za 6 měsíců příznivě ovlivňuje compliance nemocných s léčbou.

Díky za pozornost