

Ca, Mg metabolism, bone and muscle diseases

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Calcium homeostasis

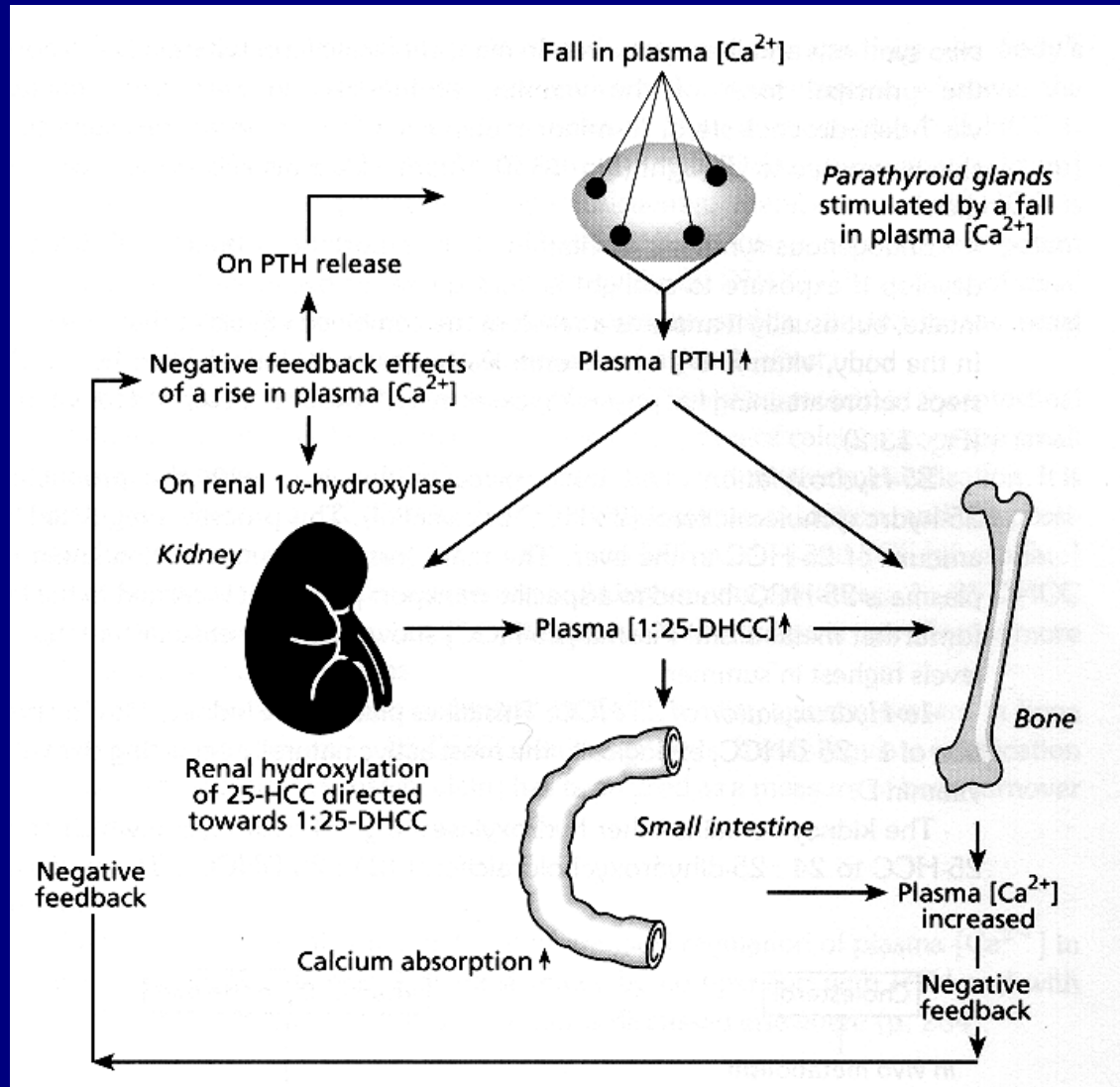
- Ca 1000g in adults
- 99% in bones (extracellular with Mg, P)
- Plasma/intracellular concentration as
total 10^{-3} mol/l water
- Intracellular concentration as
„ionized” 10^{-7} mol/l water
- Ionized Ca - muscle contraction, blood coagulation, enzyme activation, signaling, regulation of absorption/excretion

Calcium homeostasis

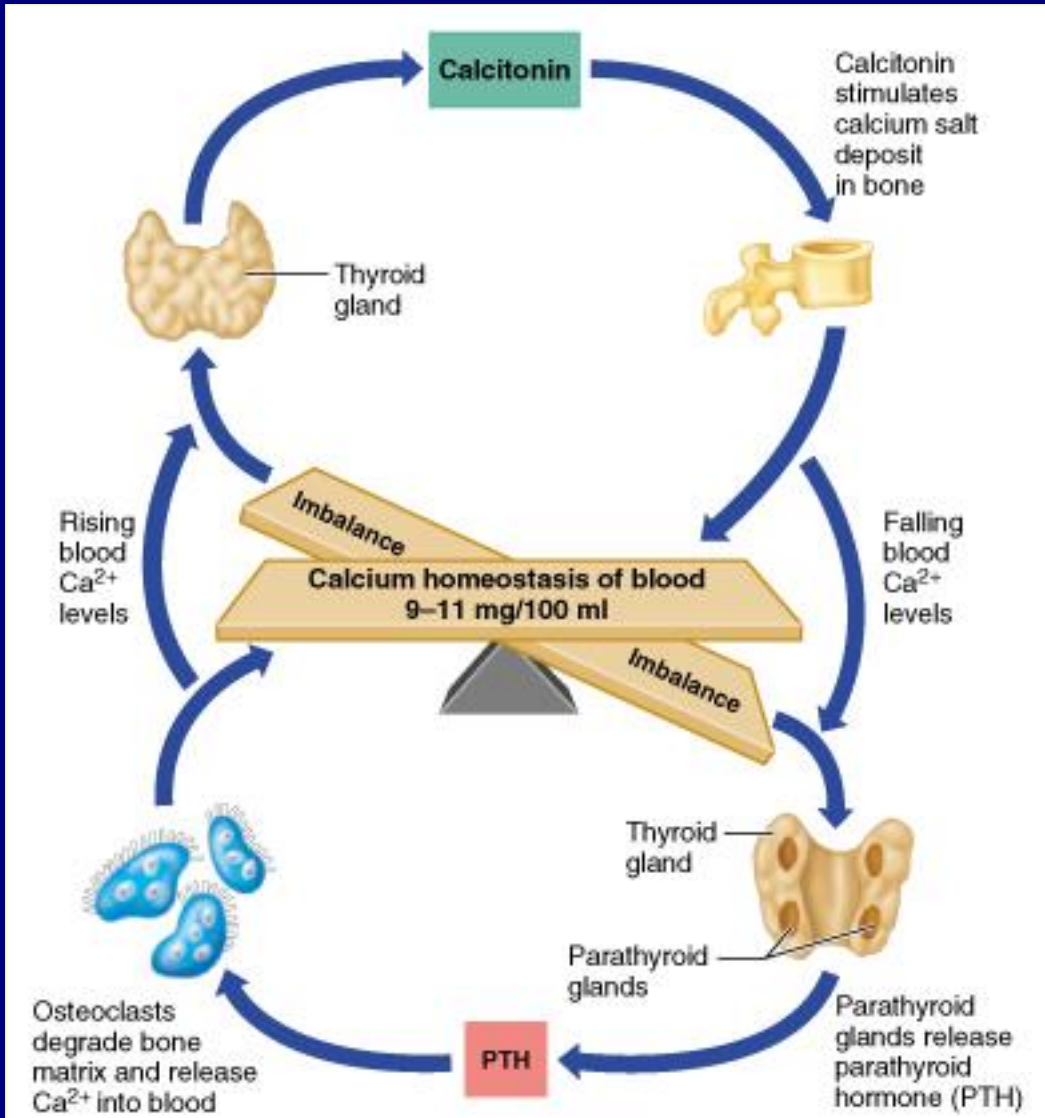
- Parathyroid hormone (peptide) in PTH gland
 - Ca release from bones (osteoclast)
 - Increased 1-alpha hydroxylation of vitamin D in kidneys (1:25DHCC)
- 1:25DHCC
 - Increased Ca absorption in gut
 - Increased mineralization in bones (osteoblast)
- Calcitonin (katalcalcin) in C-cells
 - Decreased Ca release from bones
 - Increased Ca (P) excretion

Calcium homeostasis

**PTH half life:
4 minutes!**



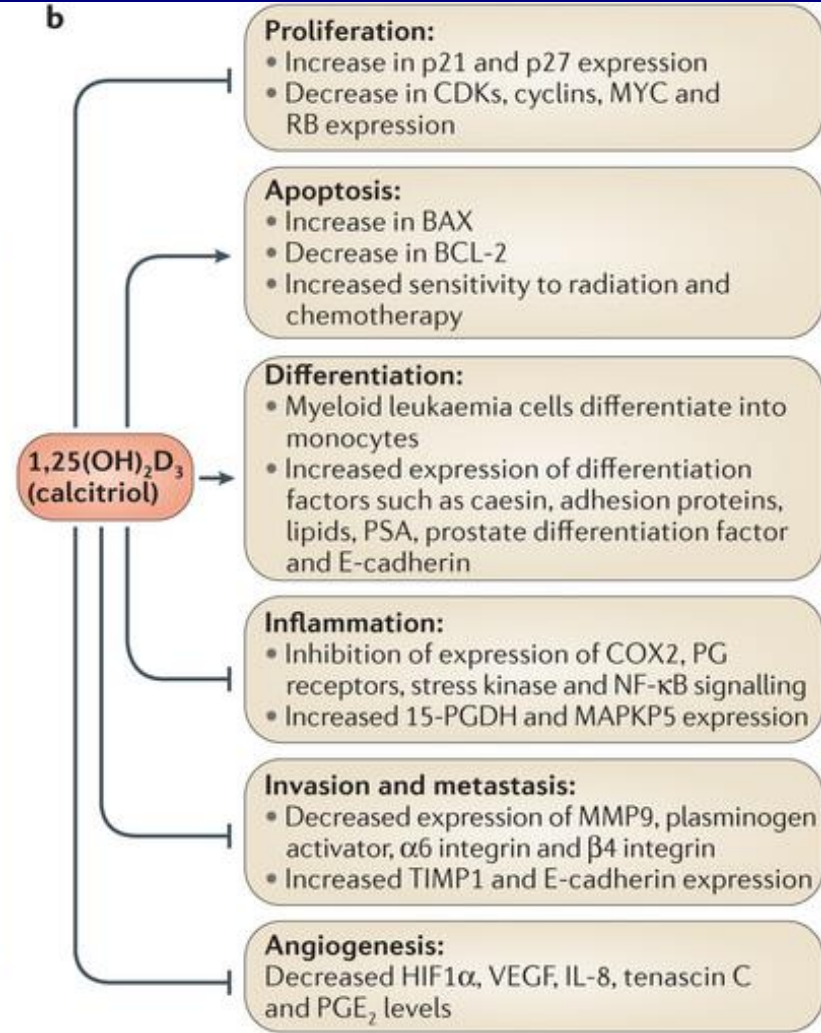
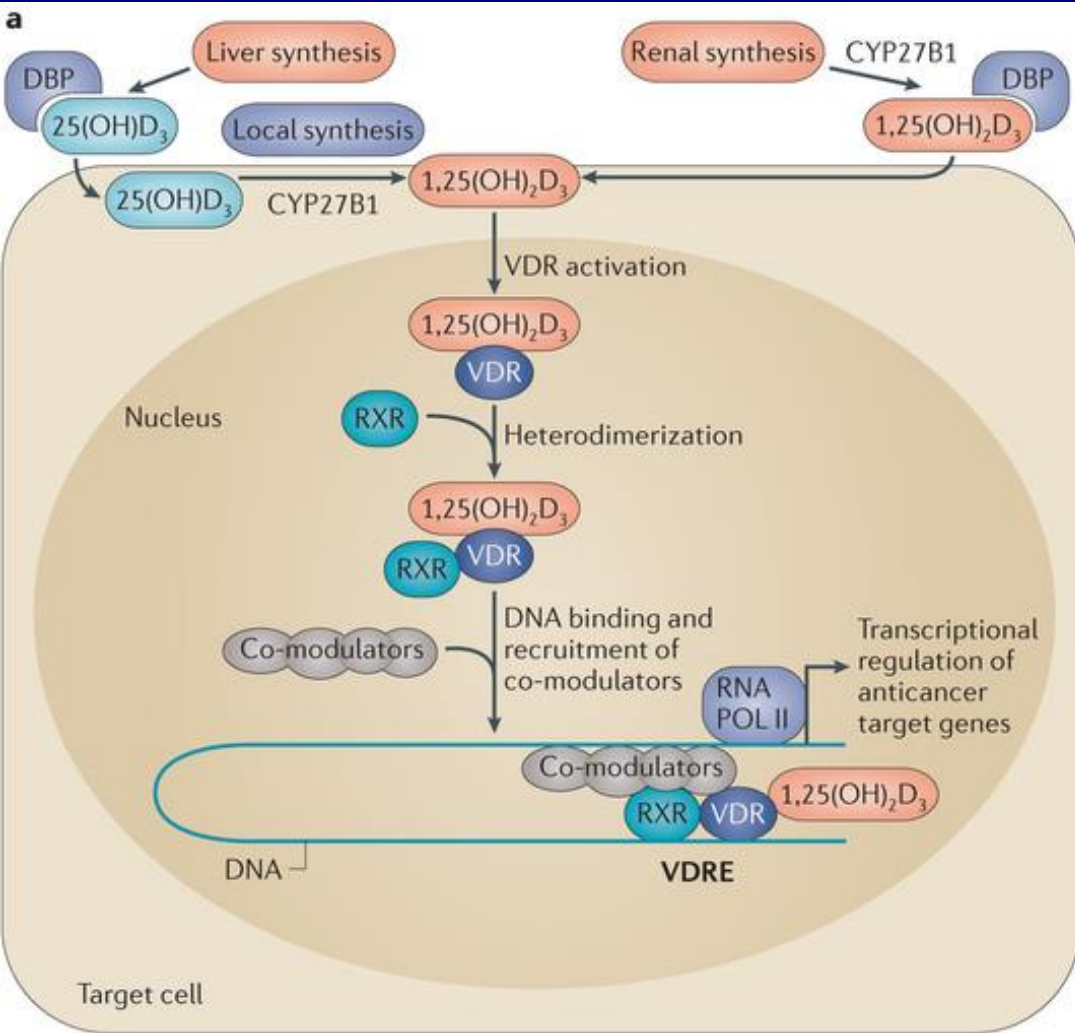
Calcium homeostasis

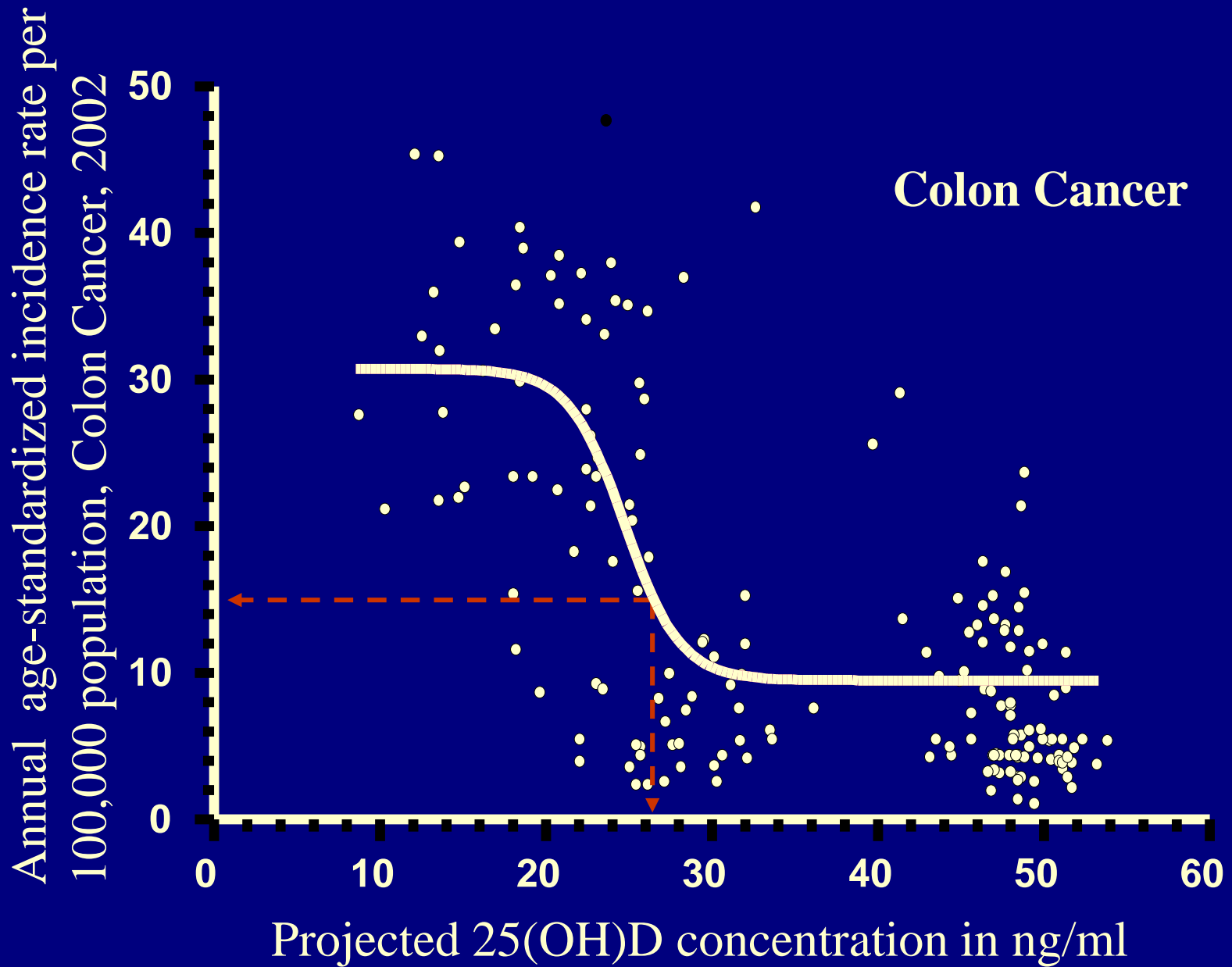


Calcitonin:
tumor marker

Procalcitonin:
sepsis marker

Beneficial effects of vitamin D





Source: GLOBOCAN Database of the International Agency for Research on Cancer.
<http://www-dep.iarc.fr/globocan/database.htm>.

Composition of bone

- Minerals ~ 65% dry weight
- Matrix ~ 35% dry weight
- Cells
- Water

Hydroxyapatite

Collagen 90%

Other proteins

Lipids, sugars

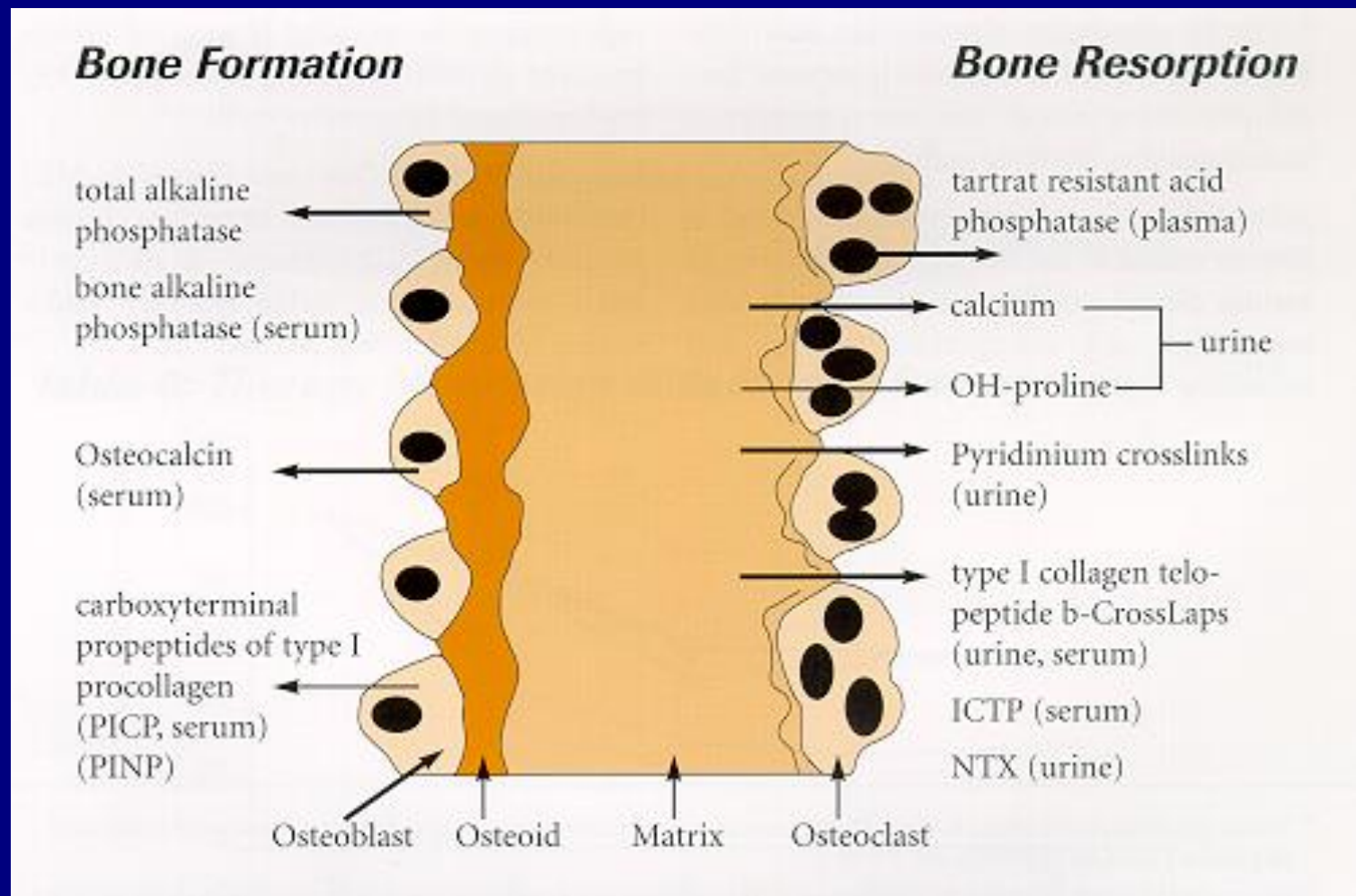
Osteoblasts

Lining cells

Osteocytes

Osteoclasts

Biochemical markers of bone formation and resorption



Interpretation of plasma Ca values (2.10-2.60 mmol/l total)

Fractions of plasma Ca	Fraction as % of total Ca
Ionized calcium (Ca²⁺)	50-65
Protein (albumin) bound Ca	30-45
Complexed Ca	5-10

Influence of plasma albumin on total Ca

Influence of H⁺ on ionized Ca (respiratory alkalosis - tetany)

Lab data useful in assessment of disorders in Ca metabolism

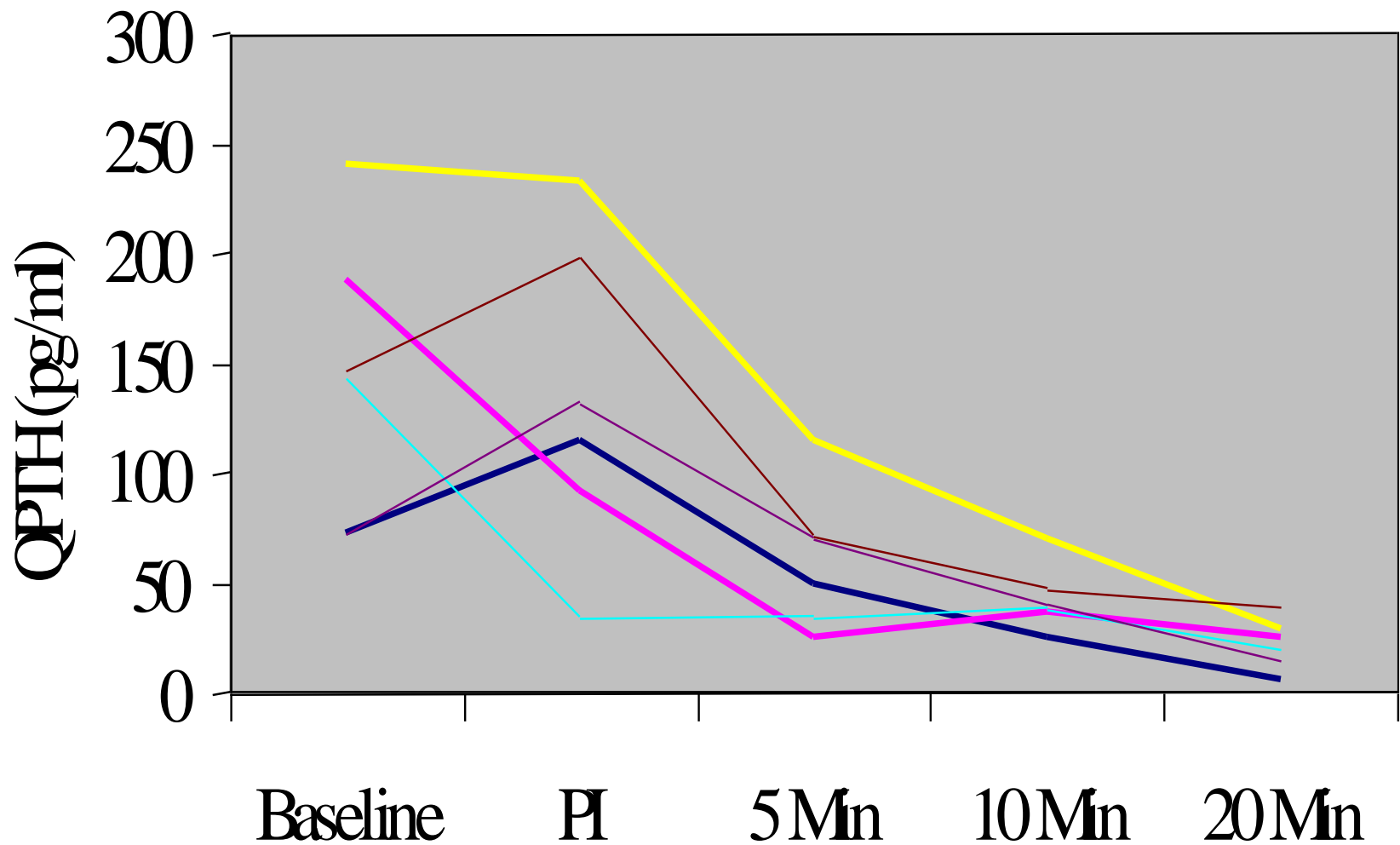
- Plasma: Ca, ionized Ca, P
Kidney function tests
ALP, bone specific ALP
Acid base balance
Total protein, albumin
Parathormon, 25-HCC
- Urine: Ca, P excretion/day or /creatinine
Type I collagen fragments

Hypercalcemia: hyperparathyroidism

Primary

Ca	Increased
P	Decreased
pH	Metabolic acidosis
Kidney function	Might be impaired
ALP	Increased
PTH	Increased (normal)
Collagen fragments	Increased

Intraoperative PTH testing



Hypercalcemia: hyperparathyroidism

Secondary

Ca	Decreased (normal)
PTH	Increased
Kidney function	Might be impaired

Tertiary

Ca, P	Increased
Kidney function	Impaired
PTH	Increased

Other hypercalcemias

- **Osteolytic bone metastases**
- **Multiple myelome**
- **Vitamin D overdose**
- **Thyreotoxicosis**

Hypocalcemia

- **Hypoalbuminemia**
- **Malabsorption**
- **Vitamin D deficiency (kidney disease)**
- **Low PTH (after surgery) or resistency**
- **Acute pancreatitis, alkalosis**
- **Ca replacement therapy with normal albumin concentration (tetany)**

Magnesium metabolism

- 24 g in adults, mostly intracellularly
- Plasma: 0,7-1,1 mmol/l (30% protein bound)
- Deficiency: rare, develops slowly

Functional test (oral)

24h urinary Mg - baseline excretion

24h urinary Mg - after oral administration

Functional test (intravenous)

48h urinary Mg (>90% should be excreted)

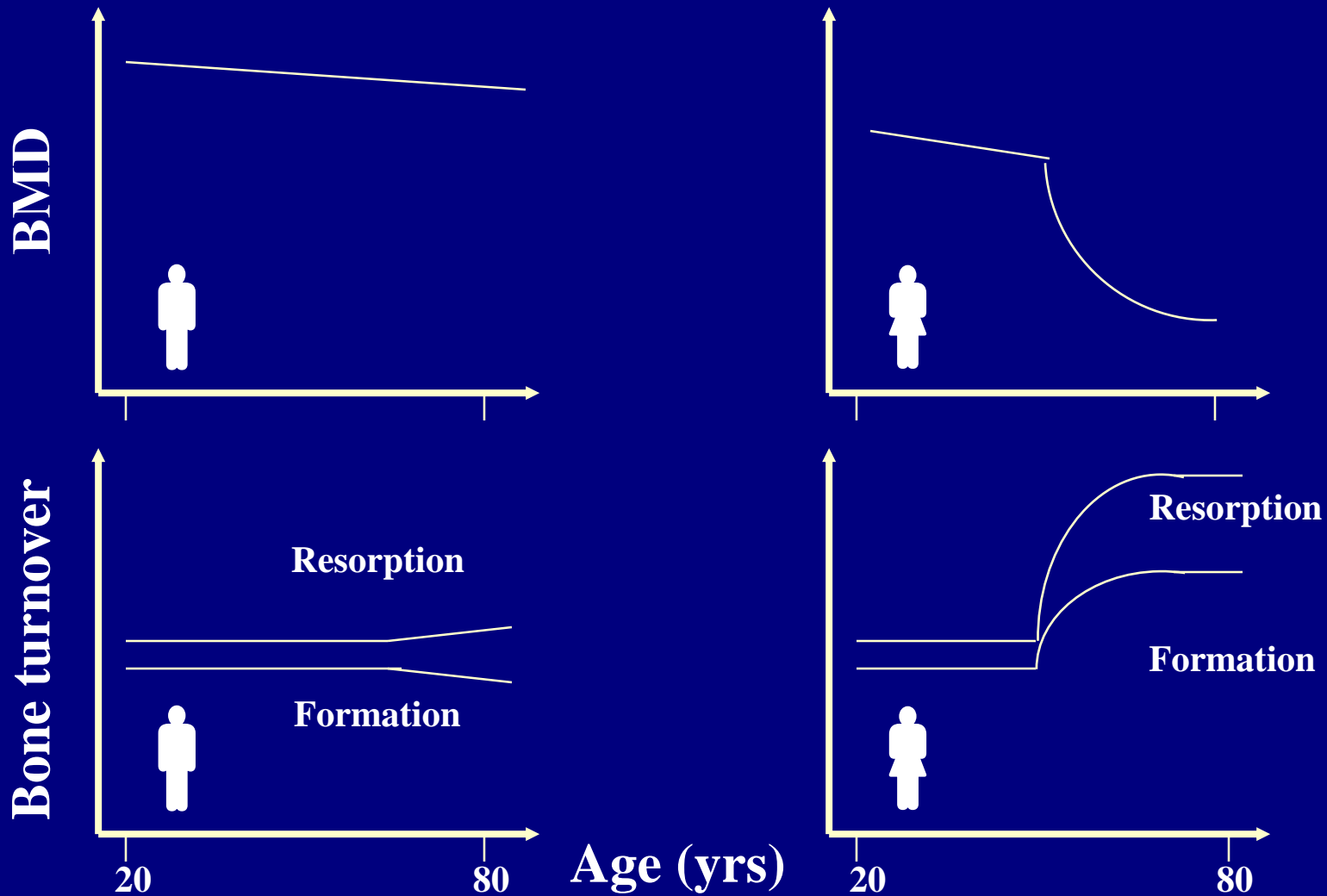
Bone remodelling

- **Bone turnover is characterised by two metabolic processes**
 - **formation of new bone (osteoblasts)**
 - **resorption of old bone (osteoclasts)**
- **Bone mass density (BMD) depends on the balance between formation and resorption**
- **There is a continuous loss in BMD during our life span (age and sex dependent)**

Factors influencing bone turnover

- Age
- Sex
- Mineral absorption and vitamin D supply
- Function of parathyroid gland
- Biological response modifiers, hormones
- **Physical activity**
- Metabolic bone diseases (Paget's)
- Impaired kidney function
- Cancer metastasis in bone

Changes in BMD and bone turnover with age



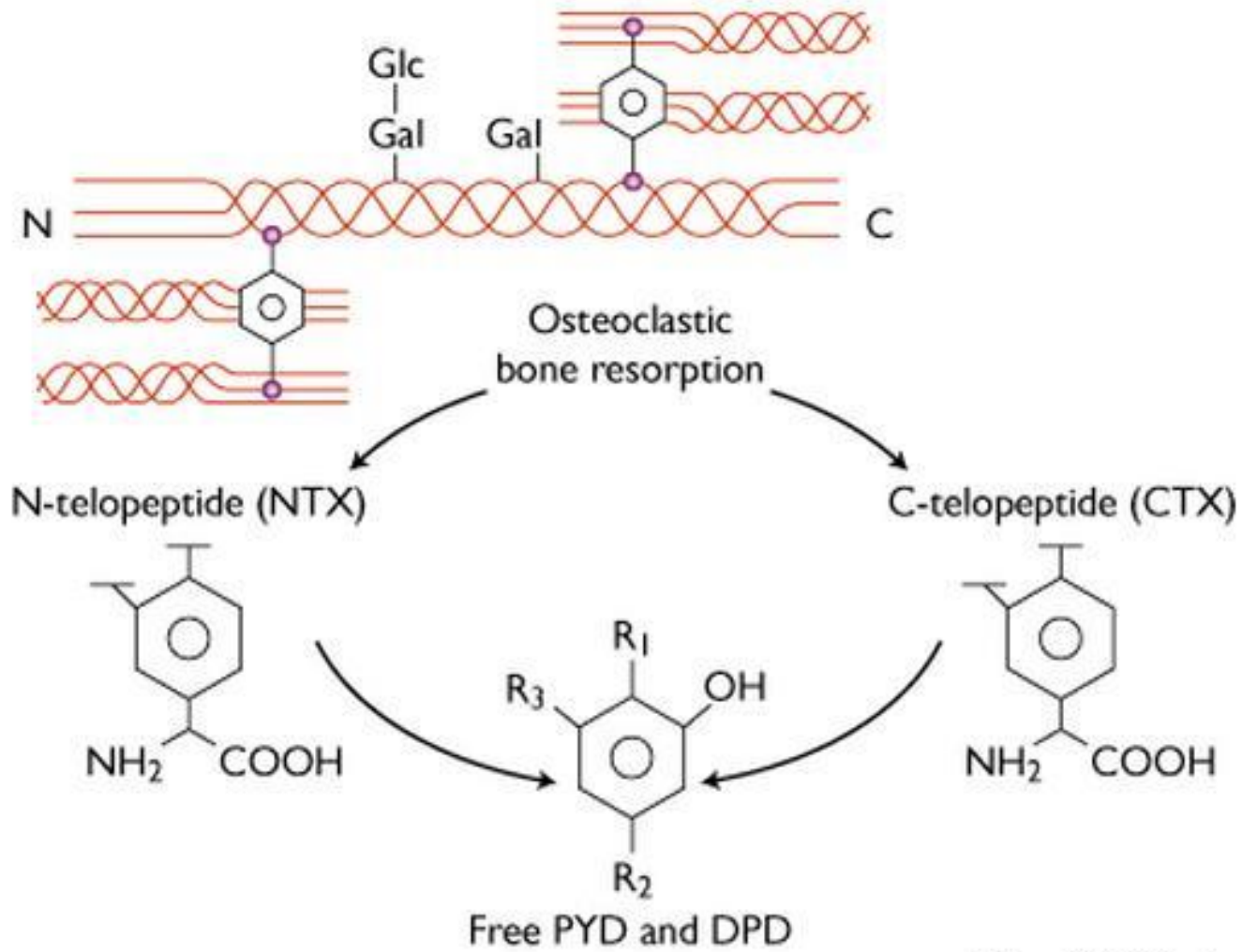
Markers of bone formation

- **Total alkaline phosphatase** - activity changes with age !
- **Bone specific alkaline phosphatase** (in osteoblasts, isoenzyme) - amount changes with age
- **Osteocalcin** (vitamin K dependent) in extracellular matrix, degrades rapidly in plasma (N-MID-osteocalcin) - increases with high bone turnover
- **Procollagen propeptides**: cleavage products during formation of type I collagen (C/N-terminal peptides)

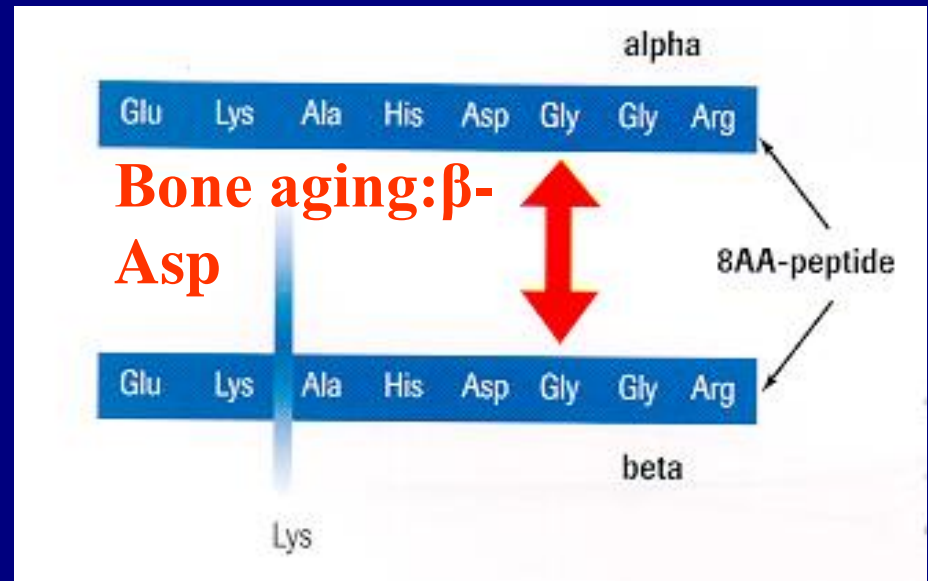
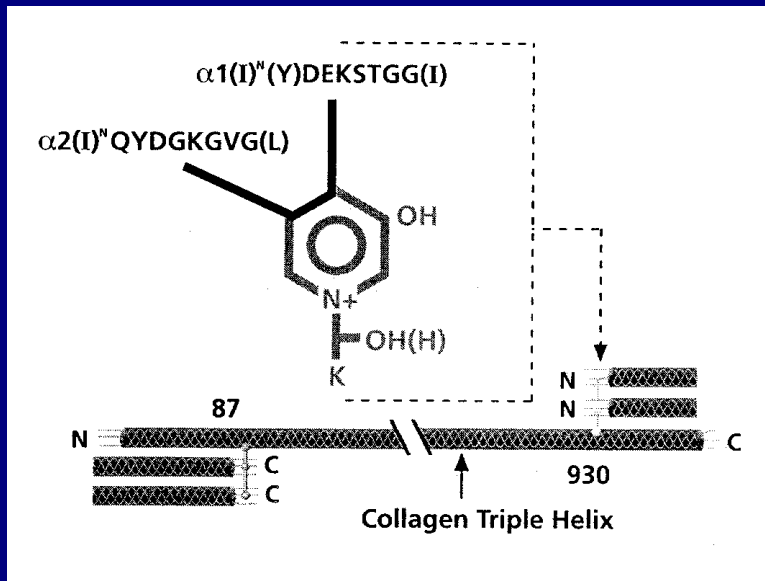
Markers of bone resorption

- **Pyridinolines (deoxy):** cross-linking collagen, cleavage products, urinary excretion corrected for creatinine - good specificity
- **N-terminal cross-links (NTx):** pyridinoline cross-link in peptide bound form, urinary excretion corrected for creatinine - good specificity
- **β -crosslaps:** C-telopeptide related collagen degradation product - urinary, serum, good specificity

Collagen type I degradation products



Structure of collagen type I degradation products



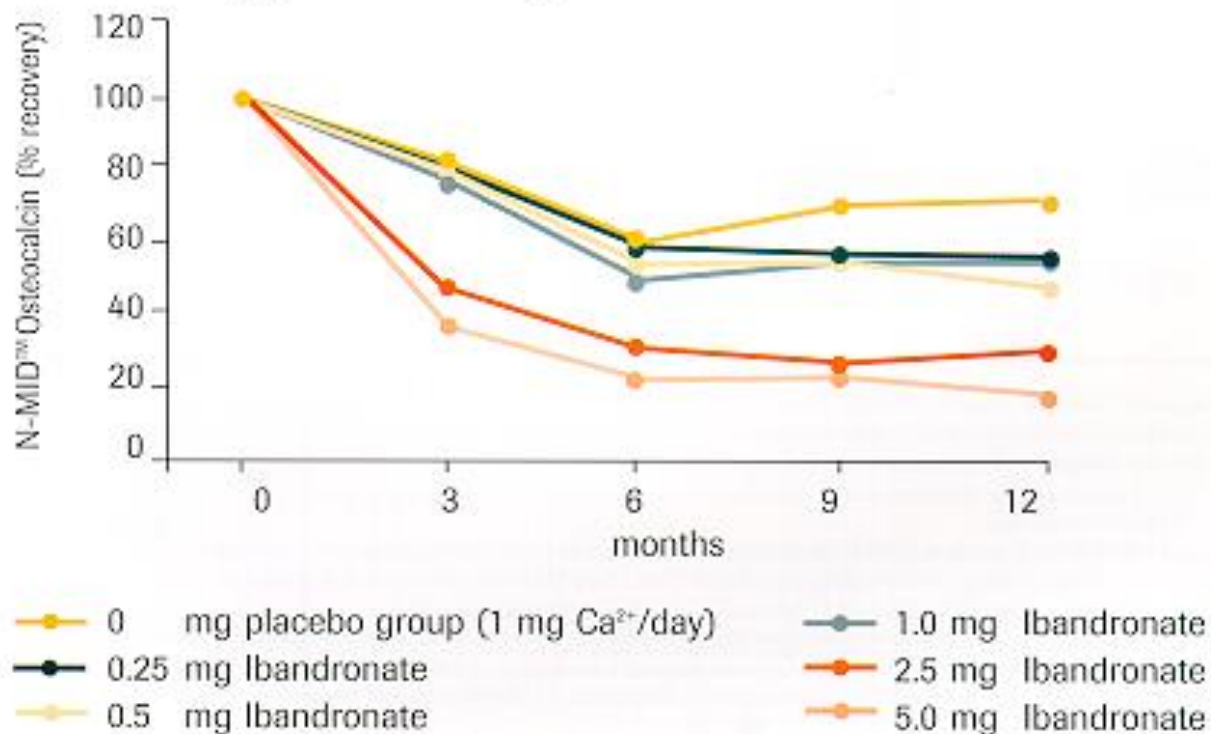
Cross-linked N-telopeptide (NTx) C-terminal cross-link (β -crosslaps)

Diurnal variation is significant

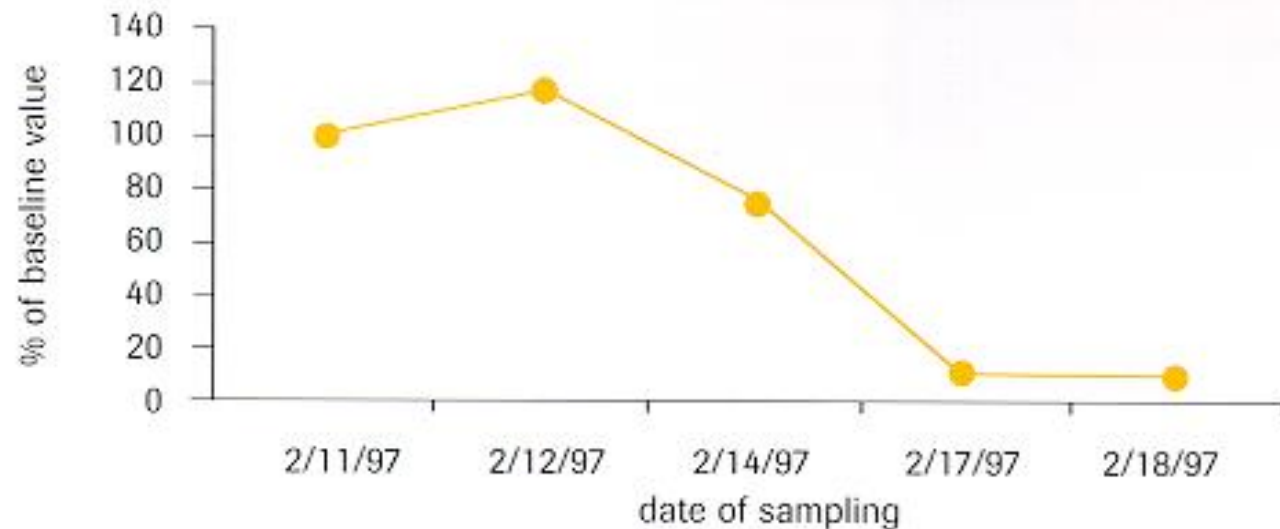
Reference ranges of bone metabolic tests done in our lab

Laboratory parameter	Reference range (adult)
Intact parathormone	0,7-5,6 pmol/l
Osteocalcin	4,0-20,0 ng/ml
Vitamin D total	48-144 nmol/l
β-crosslaps (serum)	0,010-5,94 ng/ml
Pyrilinks-D/creatinine (urine)	2,3-7,4 nmol/mmol
Total ALP	< 100 IU/l

Osteocalcin levels during antiresorptive treatment



B-crosslaps levels during bisphosphonate therapy in Paget's disease



Use of biochemical markers in osteoporosis

- **Imaging methods can not be avoided**
- **Combination of markers in early postmenopausal women can predict the rate of bone loss**
- **Rate of bone loss may predict fracture risk**
- **Monitoring the bone turnover rate is a good measure of the effects of antiresorptive therapies (HRT, bisphosphonate)**
- **Other conditions than osteoporosis can also cause increased bone turnover!**

Skeletal muscle diseases

Degenerative: hereditary muscle dystrophies

(Duchenne, Becker, neuromuscular)

**Inflammatory/autoimmune: dermatomyositis,
myasthenia gravis**

**Ischemic: circulatory problems, oxygen/nutrient
deficit**

Muscle necrosis: rhabdomyolysis (drugs!)

Malignant hyperthermia: halothane narcosis

Malignant tumors (rare)

Degenerative disorders

- **Muscle dystrophies: inherited, localized to muscle and/or nerve tissues**

Duchenne: ATP content of muscle cells decreases

release of intracellular components

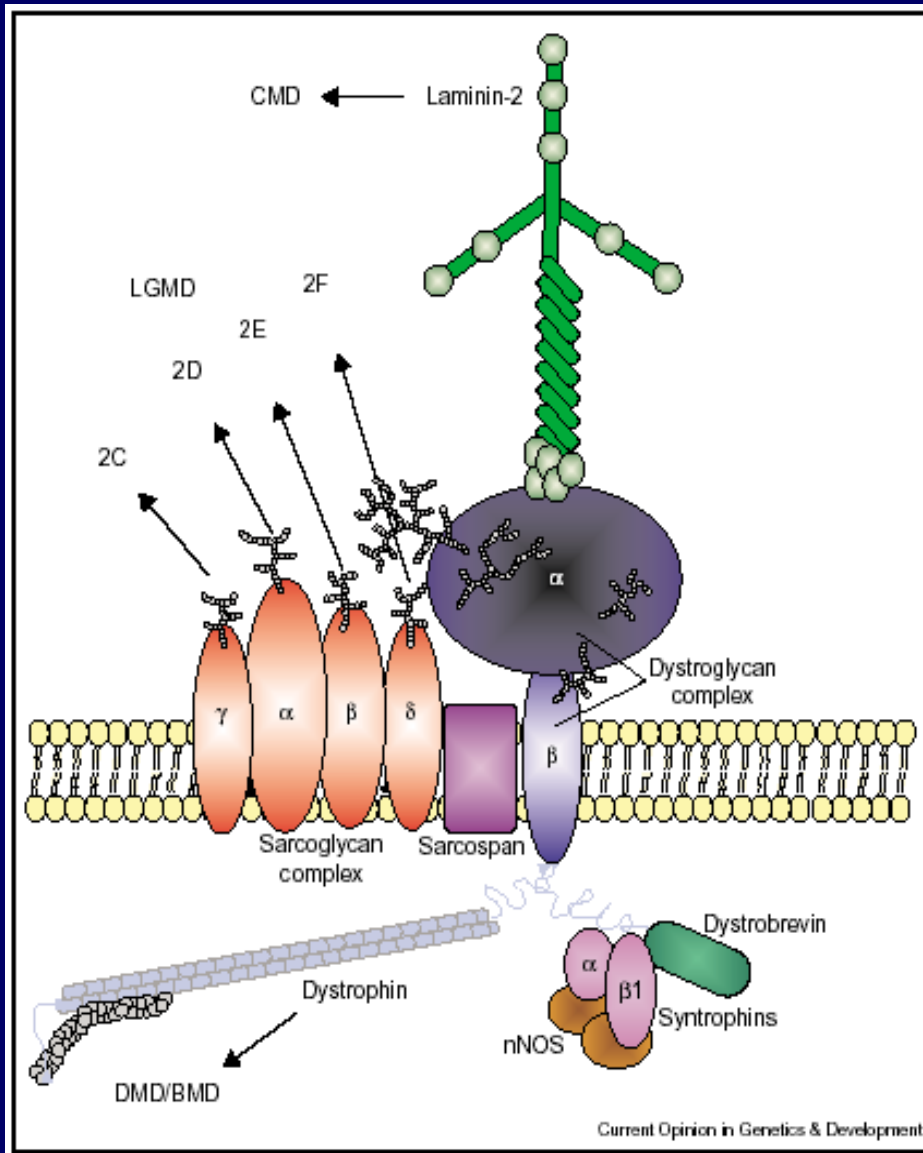
errors in creatine uptake of muscle

Dystrophin-glycoprotein complex (DGC)

Duchenne dystrophy

Gender related,
always lethal

Diagnosis: CK
Urinary creatine
PCR methods!



Adapted from Fig. 1, Durbeej and Campbell (2002)