International Symposium
Micronutrients in Milk and Dairy Products:
New Insight and Health Benefits
Paris, May 12 2011

Calcium and Phosphate:

A Duet of Ions Playing for Bone Health

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Calcium and Phosphate:
A Duet of Ions Playing for Bone Health

Bone Functions and Composition

Bone Trajectory Throuhout Life

Ca/Pi Ratio in Bone Compared to Dairy Products

Contribution of Dairy Foods to Ca and Pi Supply in the Population

Distinct Bone Pathologic Expression of Pi vs. Ca Dietary Restriction

Mineralization Process: Roles of Pi and Ca

Interactions between Ca, Pi and Bone Cells

Ca Homeostasis: Main Fluxes & Regulators

Pi Homeostasis: Main Fluxes & Regulators

} **Distinct Extraskeletal Roles**

Relative importance of Ca and Pi in Osteoporosis Management

Fulfillment of Ca and Pi RDA by Foods vs. by Pharmaceutic Preparations

Calcium and Phosphate:
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Bone Functions and Composition

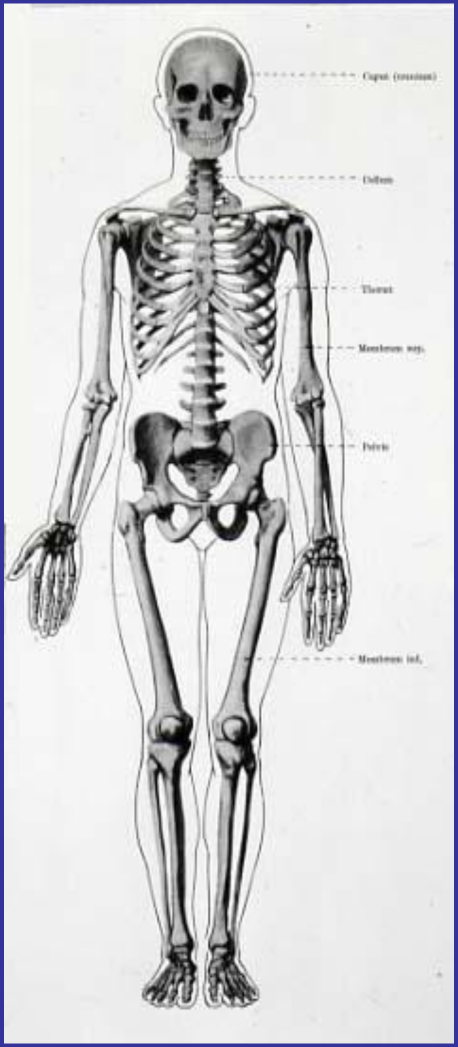
Bone is a dynamic connective tissue serving

Three main functions:

- **Mechanical** for locomotion

- **Protective** against trauma

- **Metabolic** contributing to Ca & Pi homeostasis



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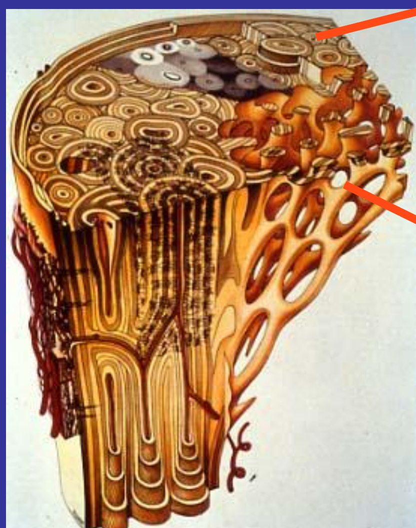
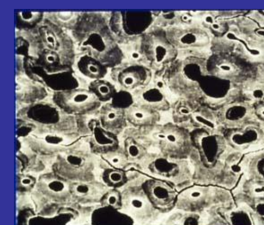
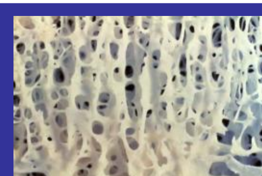
Bone Functions and Composition



Cortical, Compact Bone



Trabecular, Spongious Bone



Mineral: 60%
mainly Ca-Pi

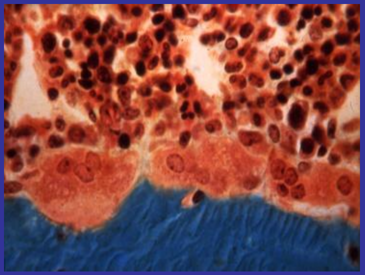
Organic Matrix: 30%
mainly proteins

Water: 10%

Bone Functions and Composition

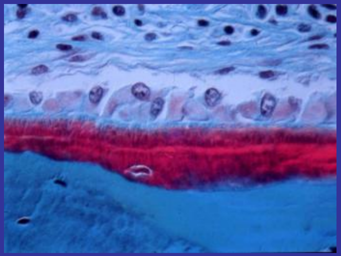
Bone Cells

Osteoclasts



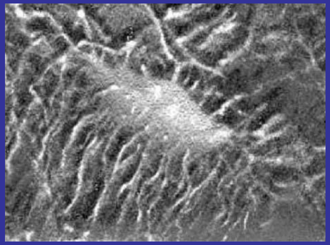
1-2%

Osteoblasts



4-6%

Osteocytes



90-95%

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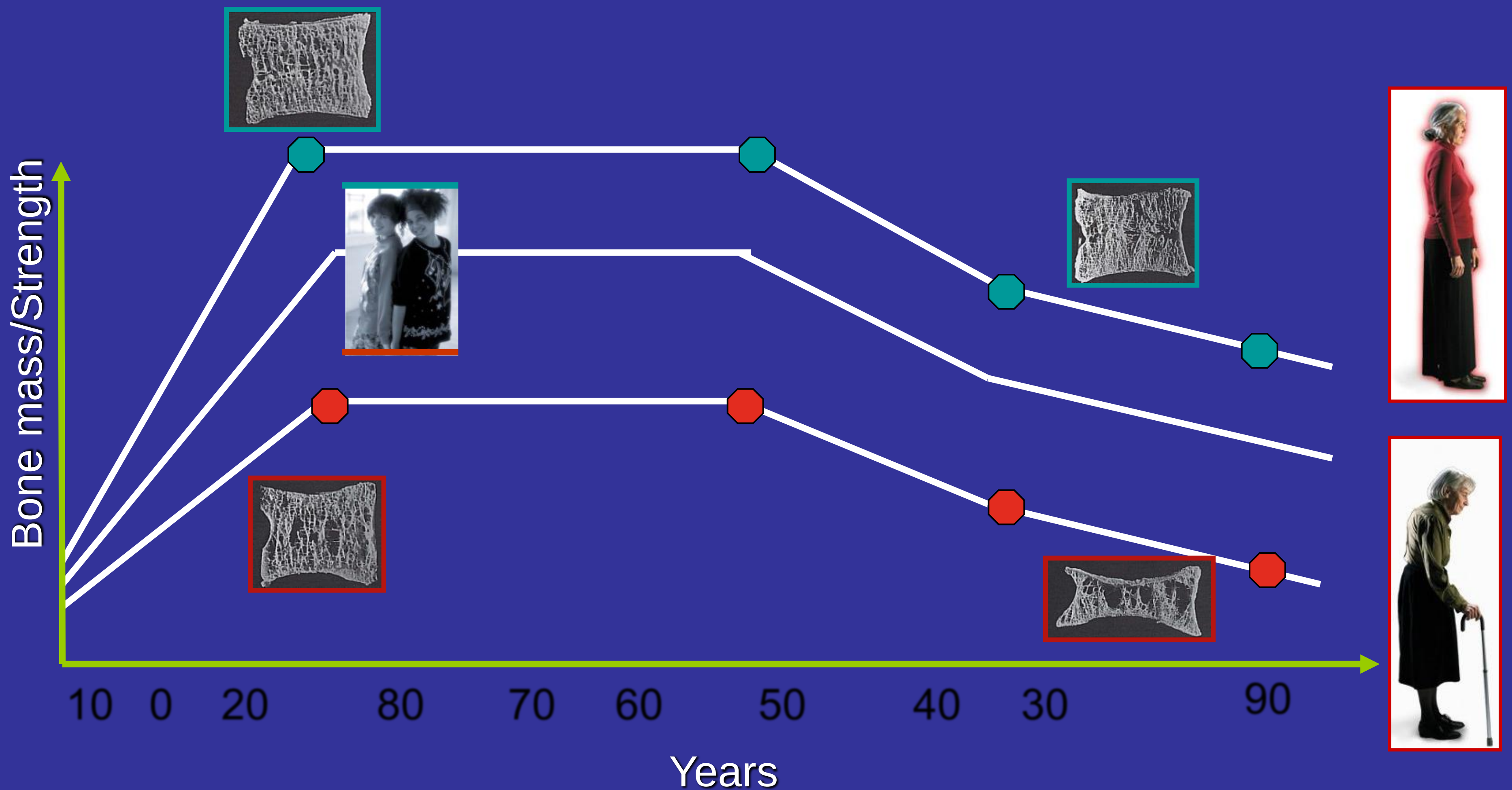
Bone Trajectory Throuhout Life



Calcium and Phosphate:
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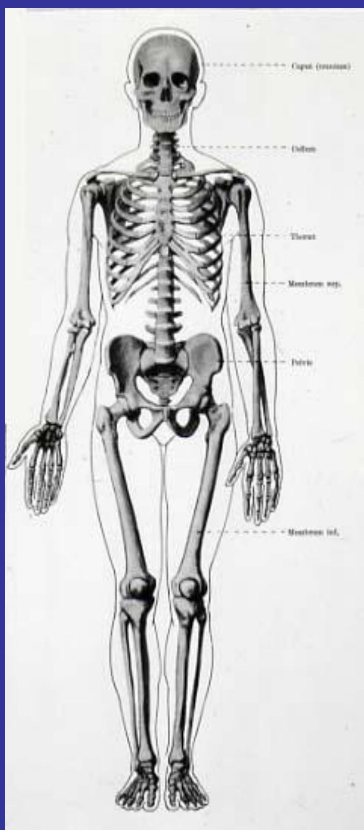
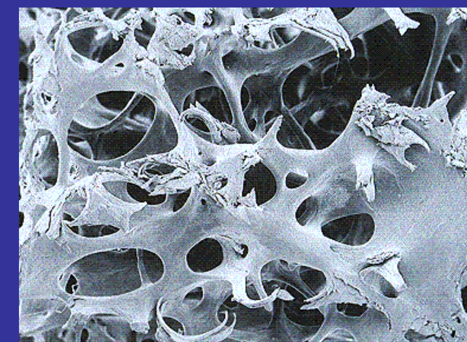
Ca/Pi Ratio in Bone Compared to Dairy Products

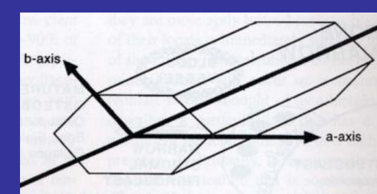


70 kg Human Adult

Mass	% Whole Body
Ca: 1300 g	99
P: 700g	80



Bone Crystal



Hydroxyapatite

$[Ca_{10}(PO4)_6(OH)_2]$

MassCa/P Ratio in Bone Compared to Dairy Products

1.9-2.4

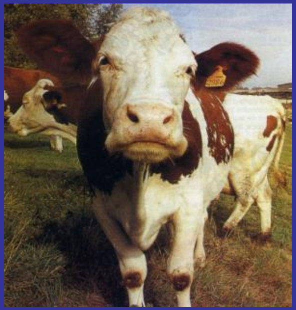
Human Milk

2.2

MassCa/P Ratio in Bone Compared to Dairy Products

1.9-2.4

Human Milk

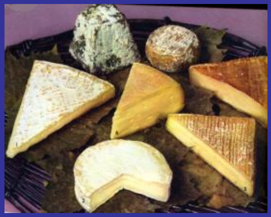


Cow Milk **1.3**

Ewe Milk **1.3**

2.2

Other Dairy Products

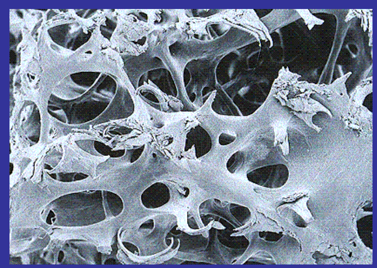


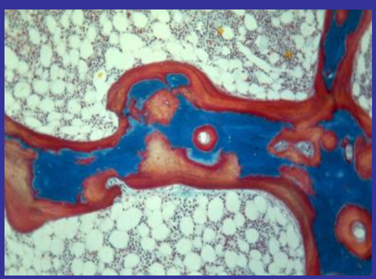
1.3

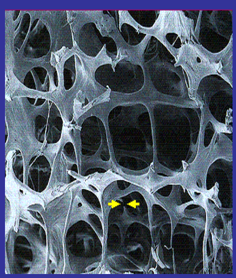
Calcium and Phosphate: A Duet of Ions Playing for Bone Health

Distinct Bone Pathologic Expression of Pi vs. Ca Dietary Restriction

Normal Ca-Pi Supply | Pi Restriction | Ca Restriction

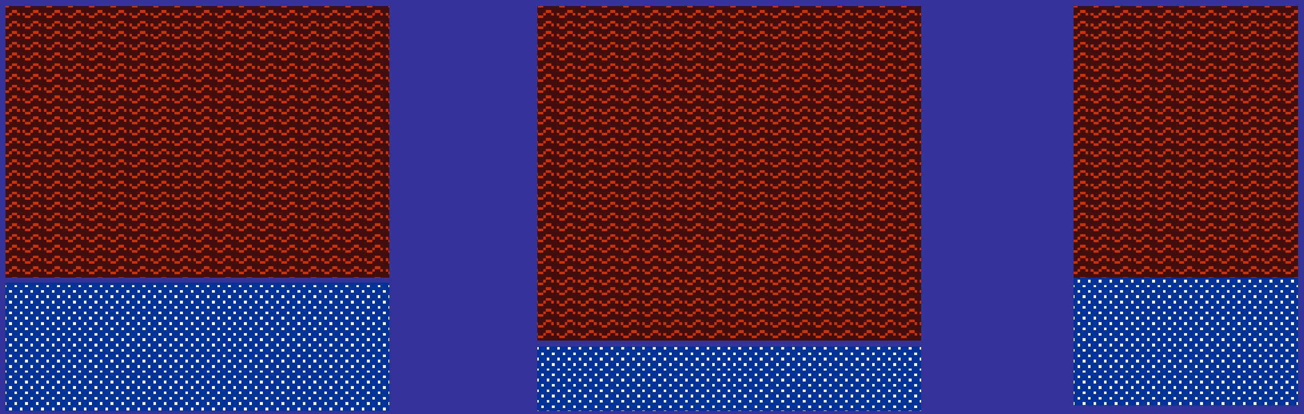






Bone Matrix

Bone Mineral



Osteomalacia | Osteoporosis

Distinct Bone Pathologic Expression of Pi vs. Ca Dietary Restriction

Low Phosphatemia Due to Pi Metabolism Disturbances Mimicks Nutritional Vitamin D Deficiency in Children: RICKETS

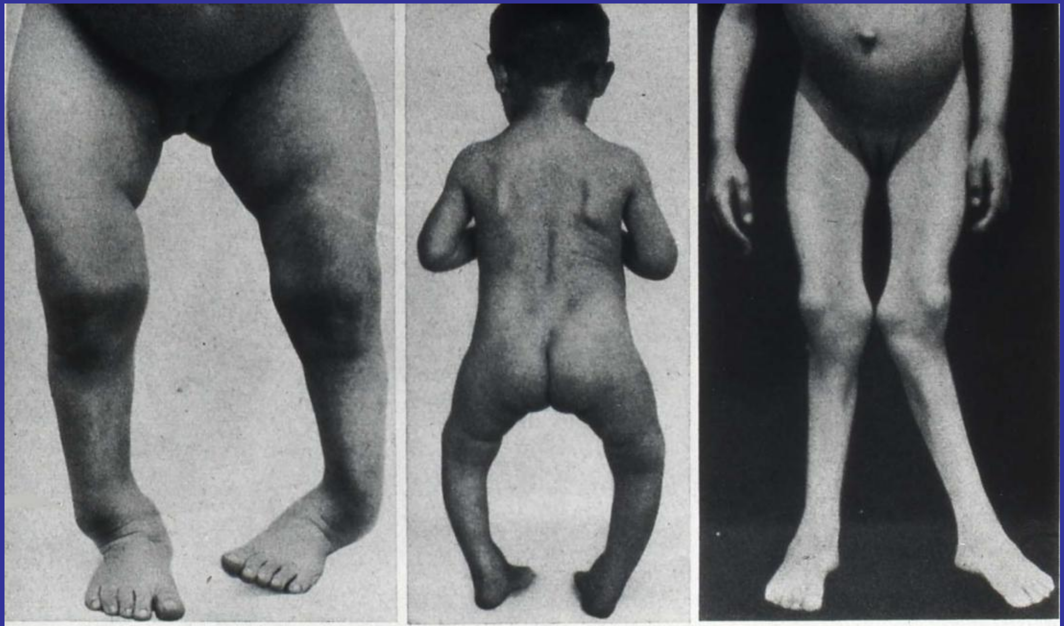


Abb. 62. Crura vara rachitica.

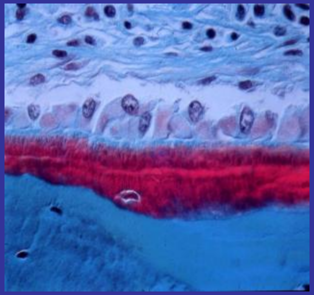
Abb. 63. Rachitische O-Beine.

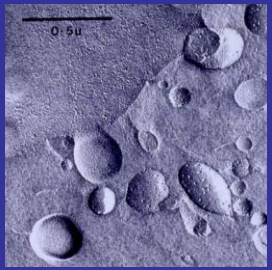
Abb. 64. Rachitis: Genua valga.

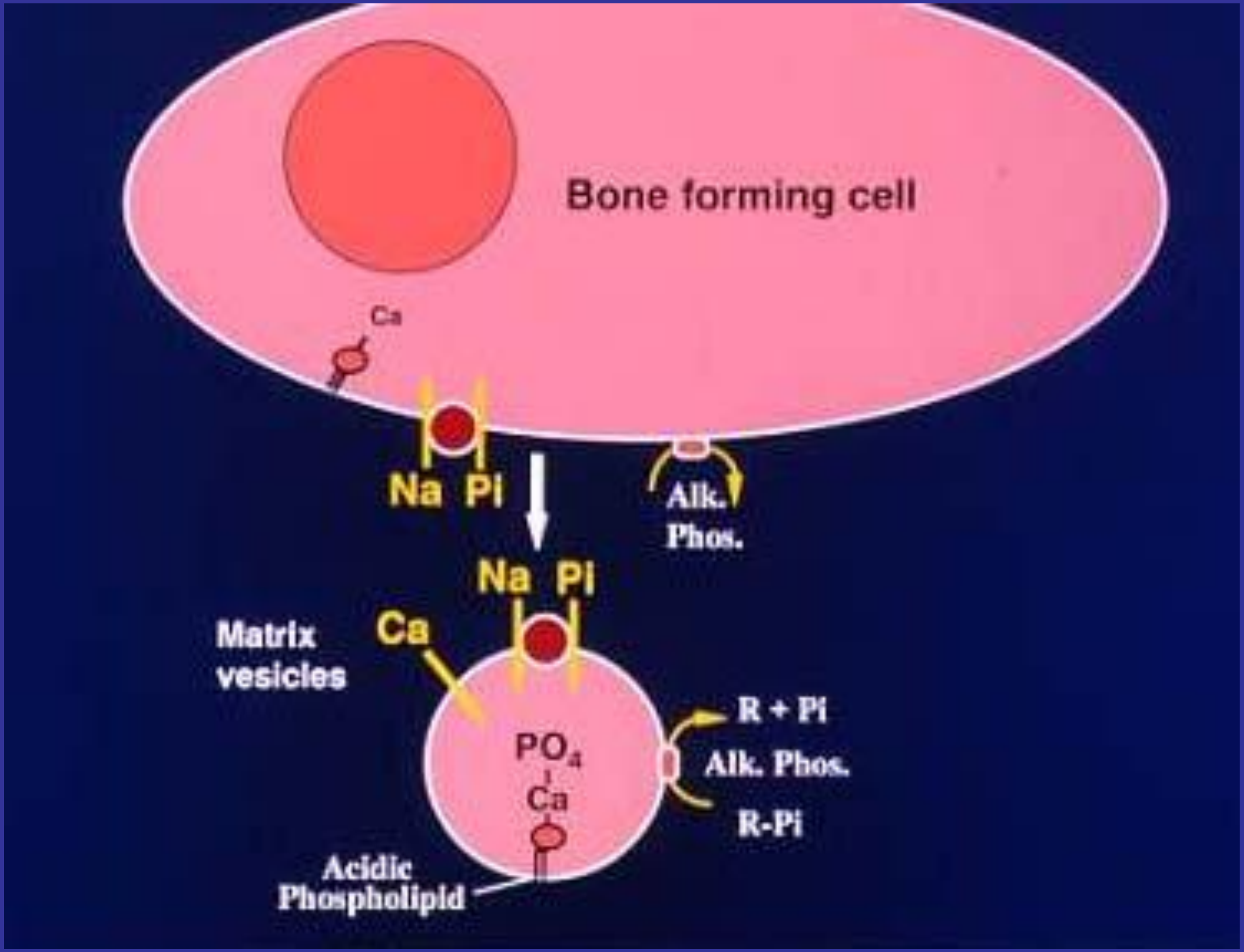
Fanconi and Wallgren Lehrbuch de Pädiatrie 1961 Benno Schwabe & Co ,Verlag Basel/Suttgart

Calcium and Phosphate: A Duet of Ions Playing for Bone Health

Mineralization Process: Roles of Pi and Ca







Adapted from Caverzasio and Bonjour, Kidney Int 1996

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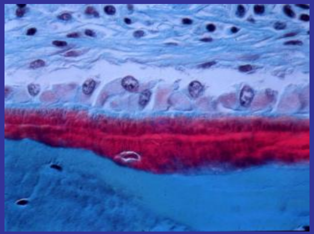
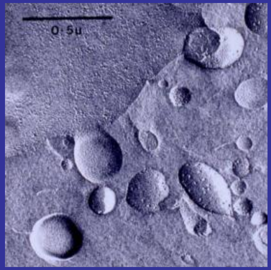
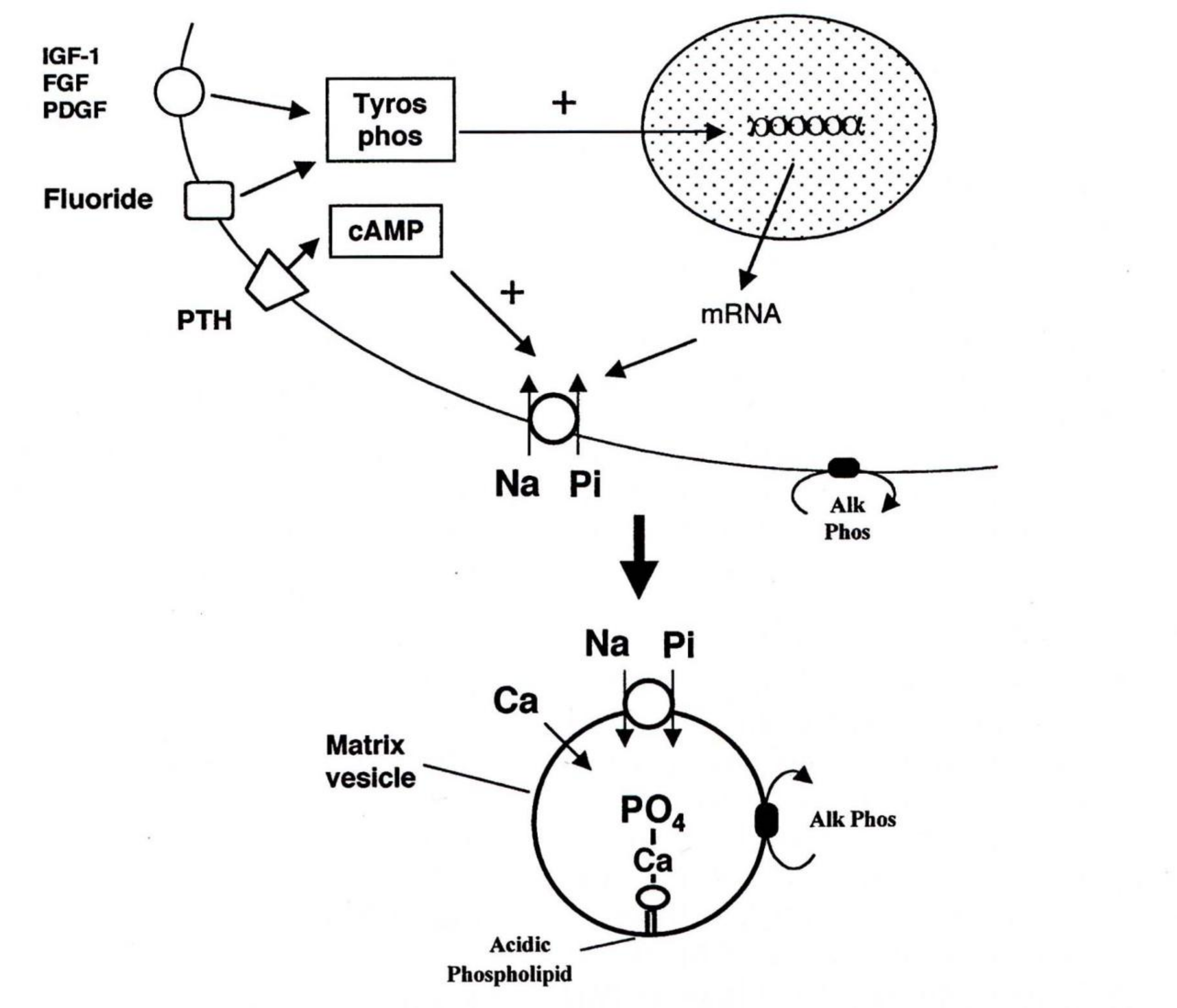
Mineralization Process: Roles of Pi and Ca

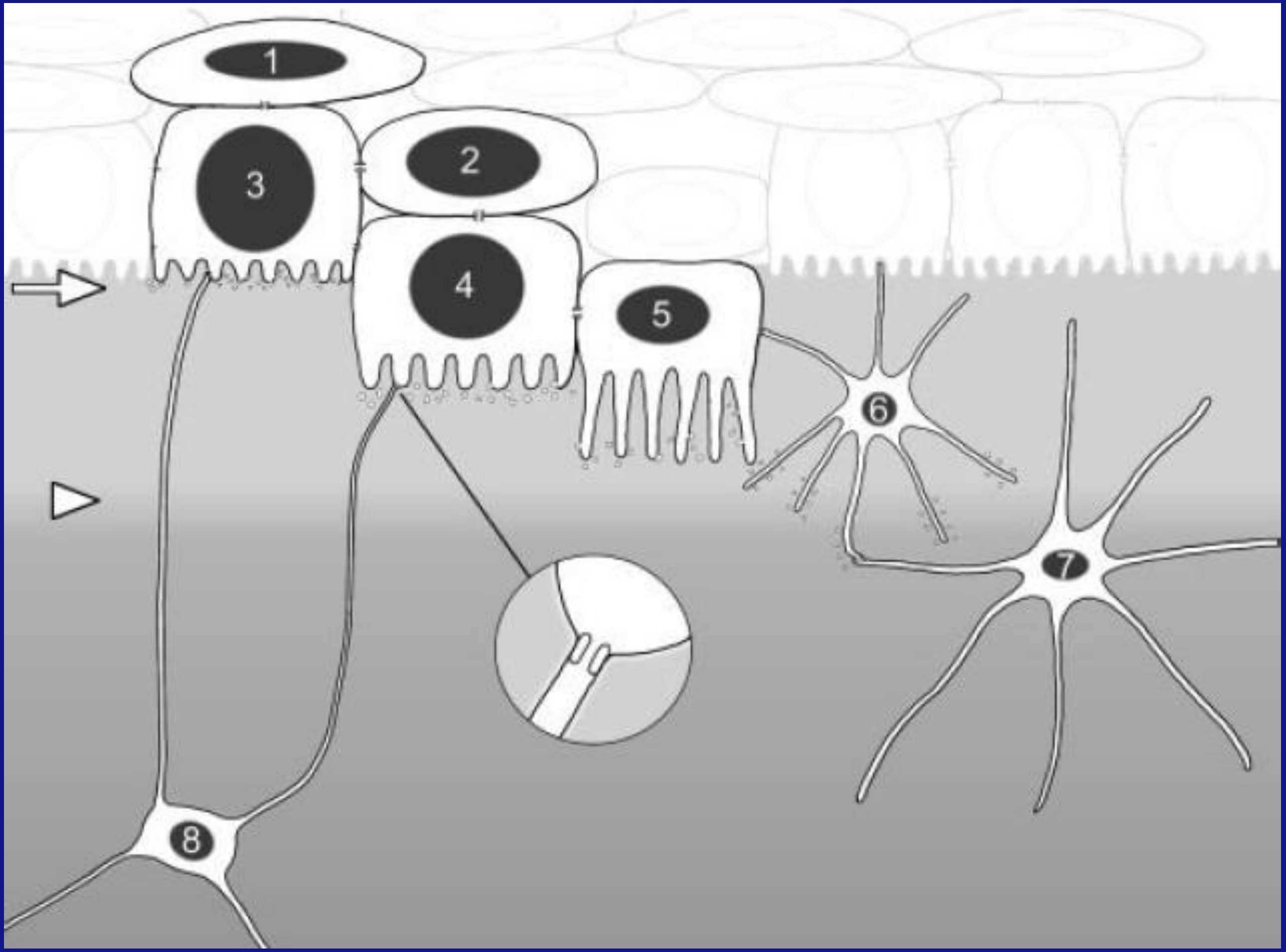






Adapted from Caverzasio and Bonjour, Kidney Int 1996

Osteocytogénèse



1 & 2 Preosteoblasts
3 Osteoblasts
4 & 5 Osteoblastic Osteocytes (Preosteocytes)
6, 7 & 8 Osteocytes

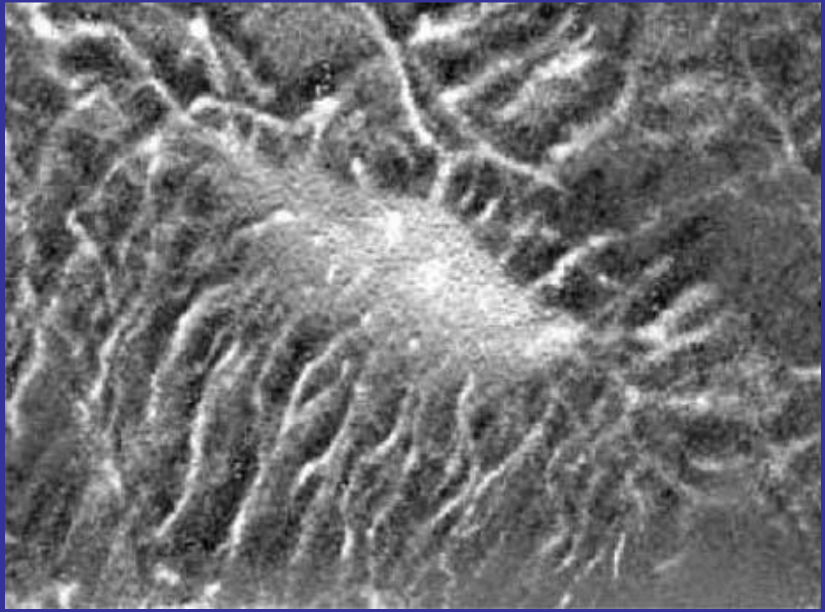
Tamara Devel. Dyn.2006

DEVELOPMENTAL DYNAMICS 235:176–190, 2006

REVIEWS–A PEER REVIEWED FORUM

Buried Alive: How Osteoblasts Become Osteocytes

Tamara A. Franz-Odendaal,[1*] Brian K. Hall,[1] and P. Eckhard Witten[1,2*]



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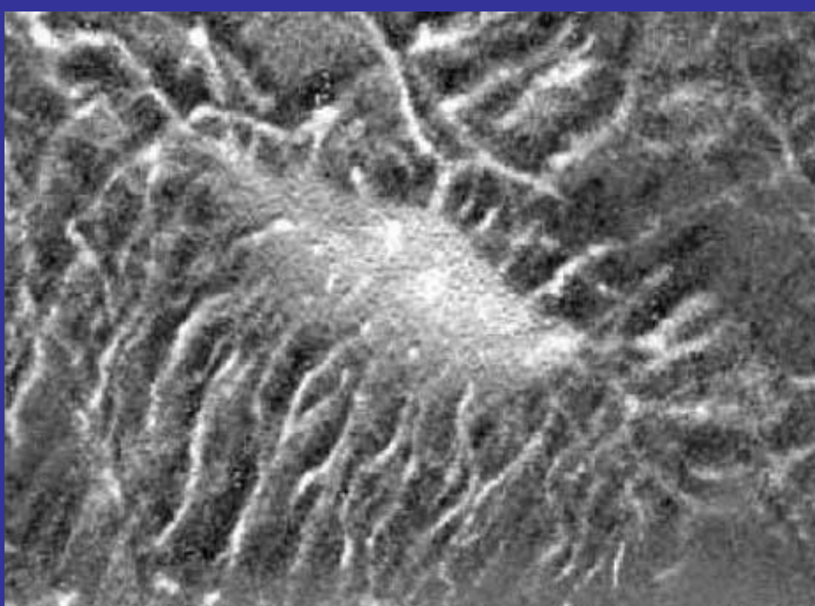
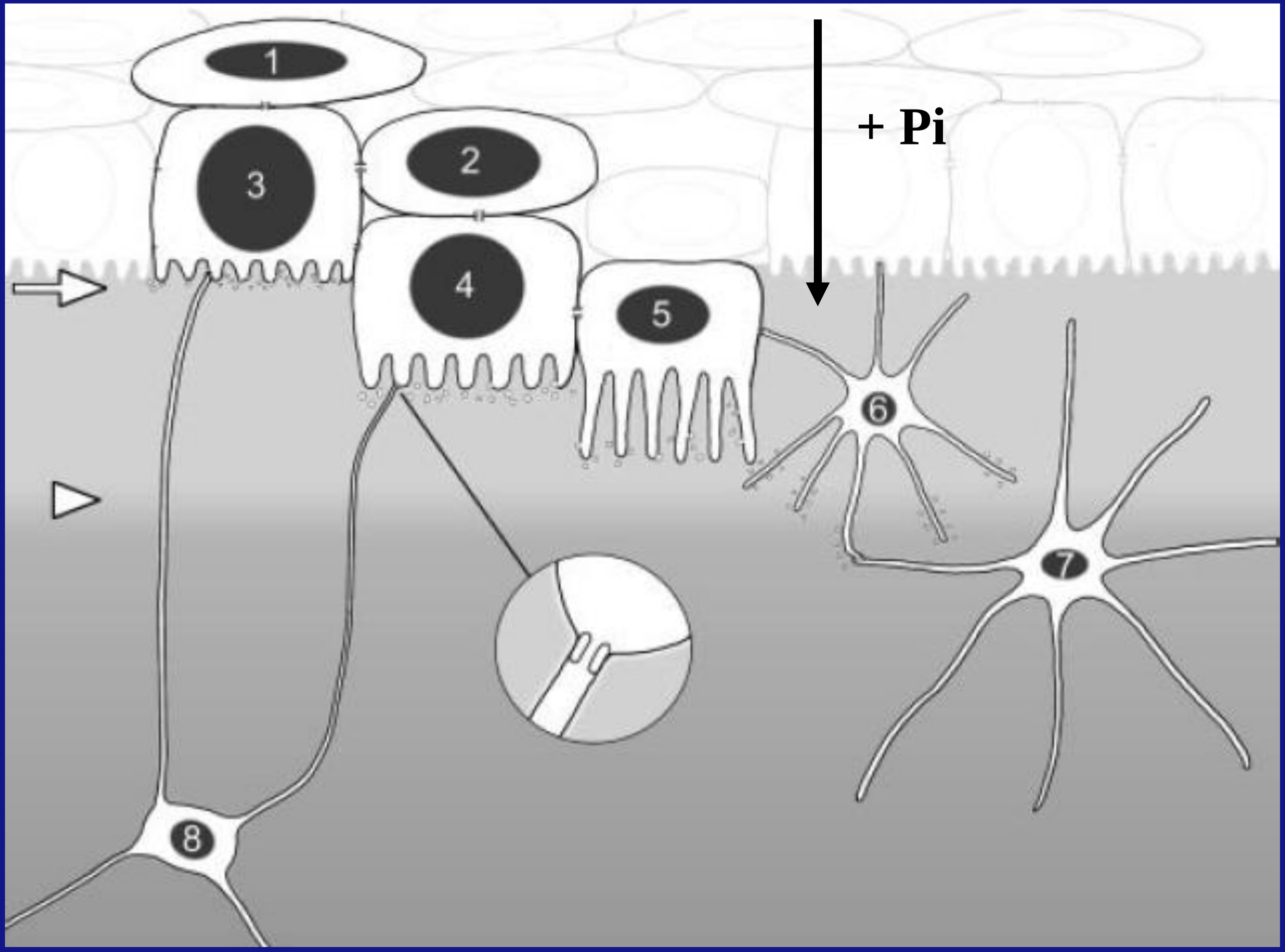


So what ?

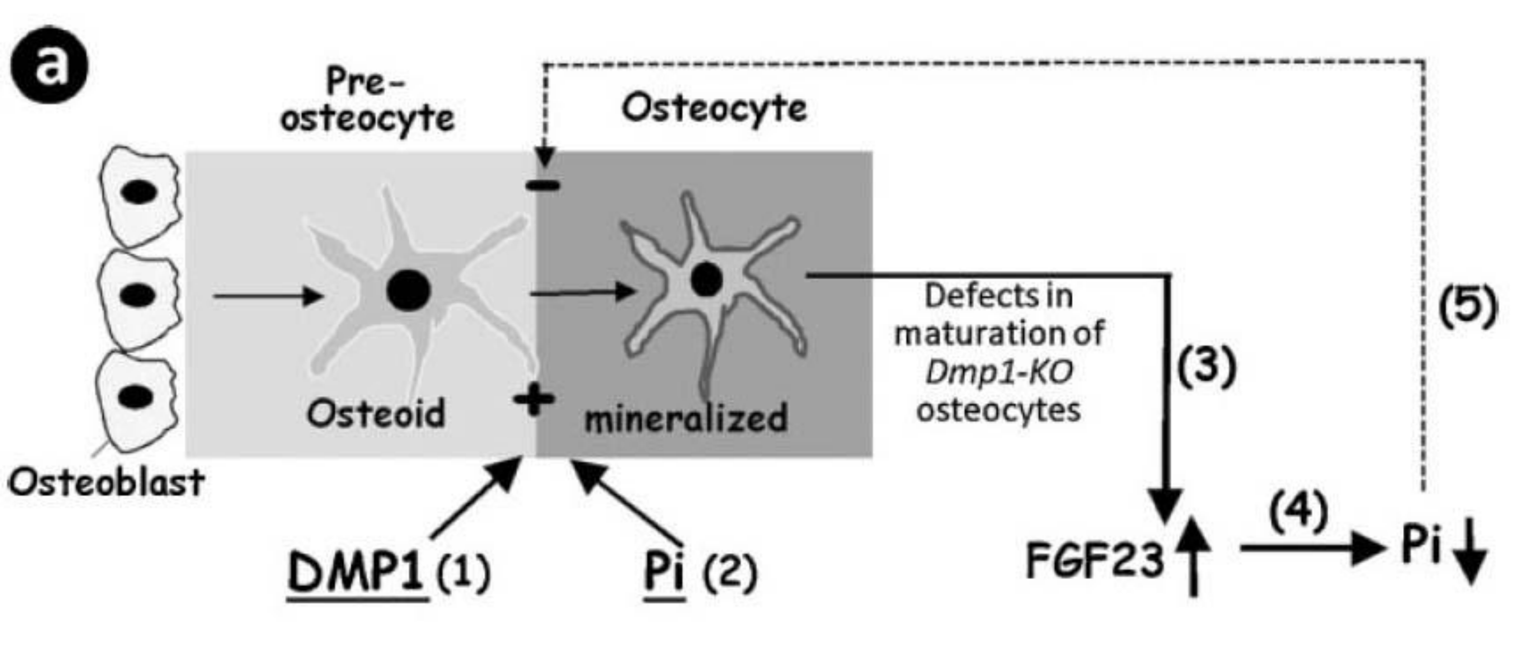
Any Role for Ca or Pi in Osteocytogenesis ?

Control by Pi of Bone Biology



Pi Dependence of:
Osteoblast
Matrix Mineralization
And
Osteocyte Maturation

Adapted from Tamara Devel. Dyn.2006 and Wang JBMR 2011



DMP1=Dentin Matrix Protein 1

FGF23=Fibroblast Growth Factor 23

Adapted from Zang JBMR 2011

QuickTime™ and a
decompressor
are needed to see this picture.

QuickTime™ and a
decompressor
are needed to see this picture.

Fukumoto. Mol Cell Endocrinol 2008

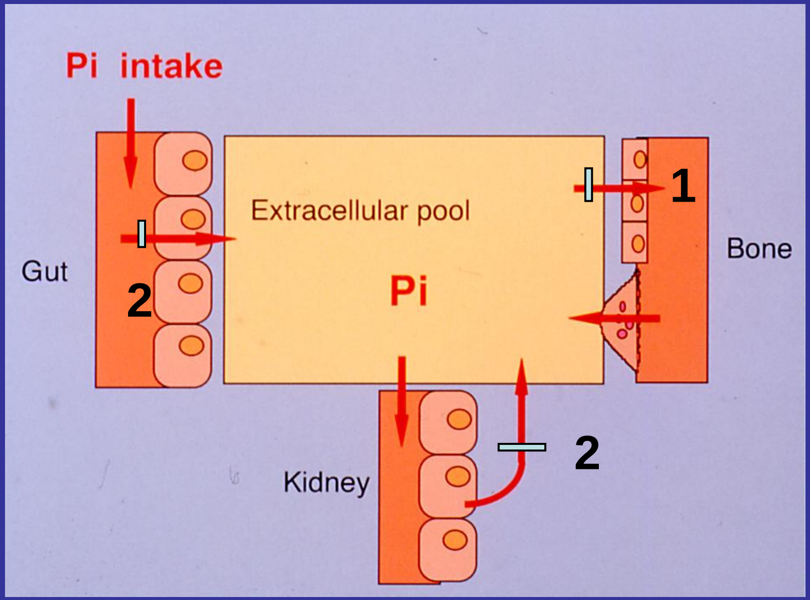
Back to the Old Seventies
and
to Physiology and Pathophysiology
with
The Concept of a Putative
Bone-Kidney Link in Pi Homeostasis

Is there a bone-kidney link
in the homeostasis of inorganic phosphate (Pi)?

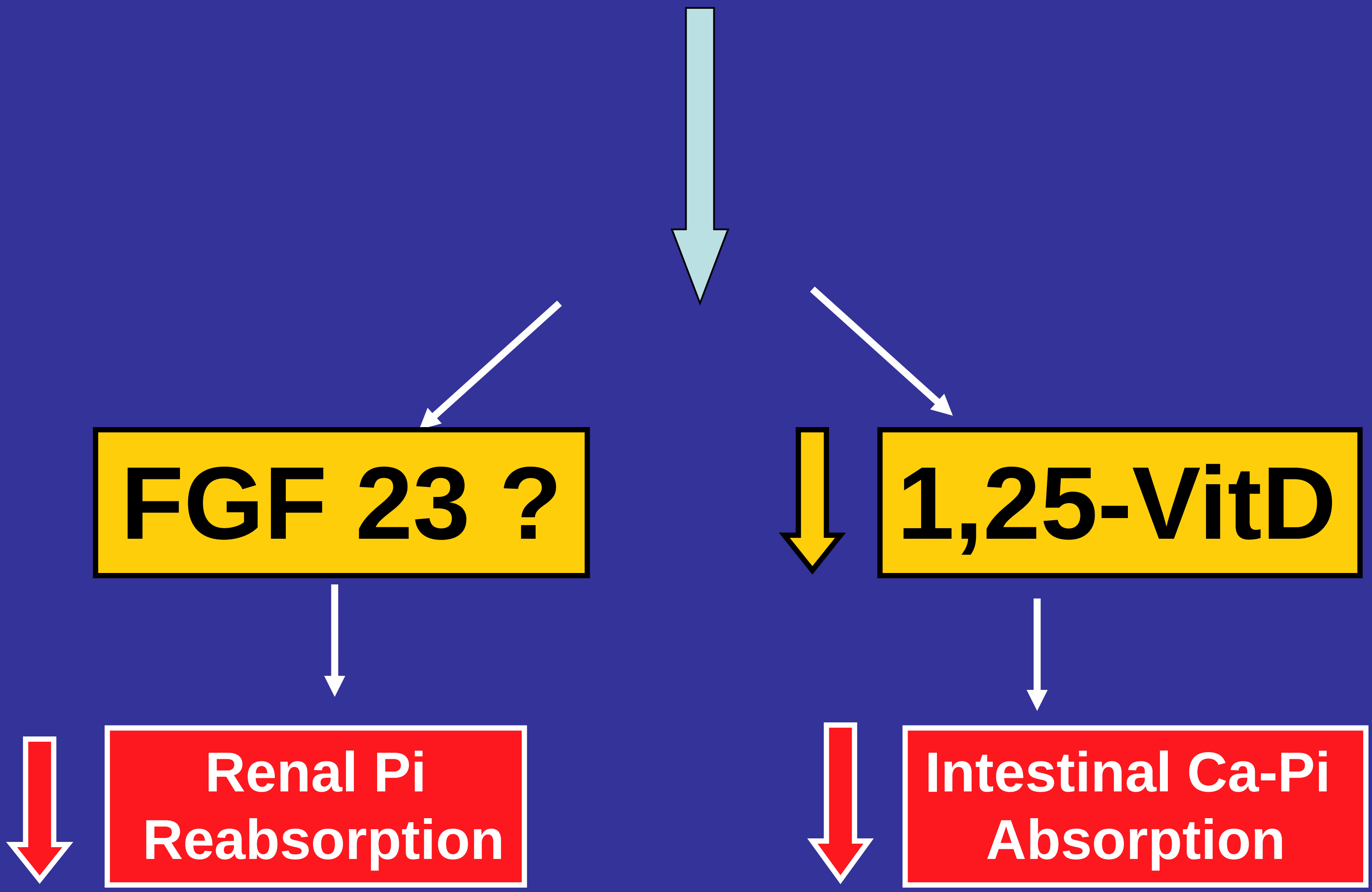
Bonjour et al. Adv Exp Med Biol 1977; 81:319-22

Controls

Mineralization Inhibiion by EHDP



Pharmacological Inhibition of Bone Mineralizatiion



Evidence for a physiological role of FGF-23 in the regulation of renal phosphate reabsorption and plasma calcitriol in healthy humans

SL Ferrari

JP Bonjour

R Rizzoli

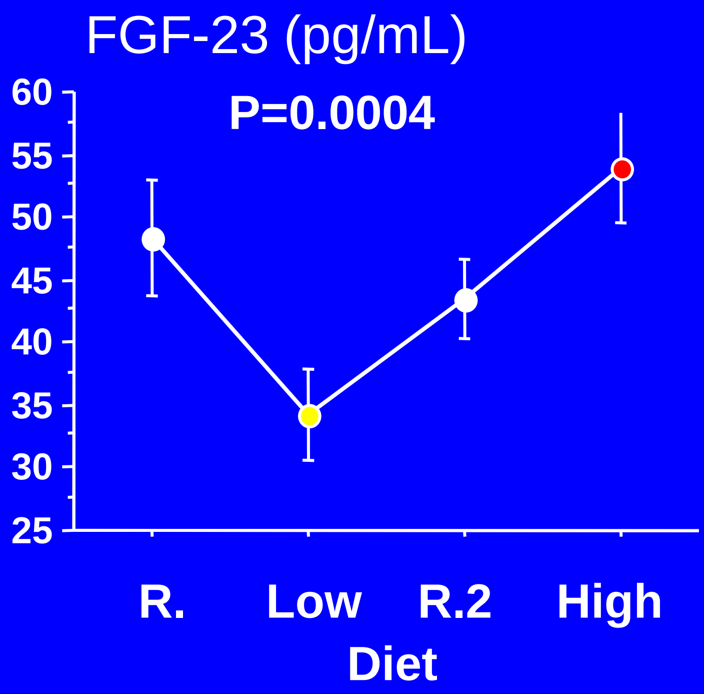
Division of Bone Diseases

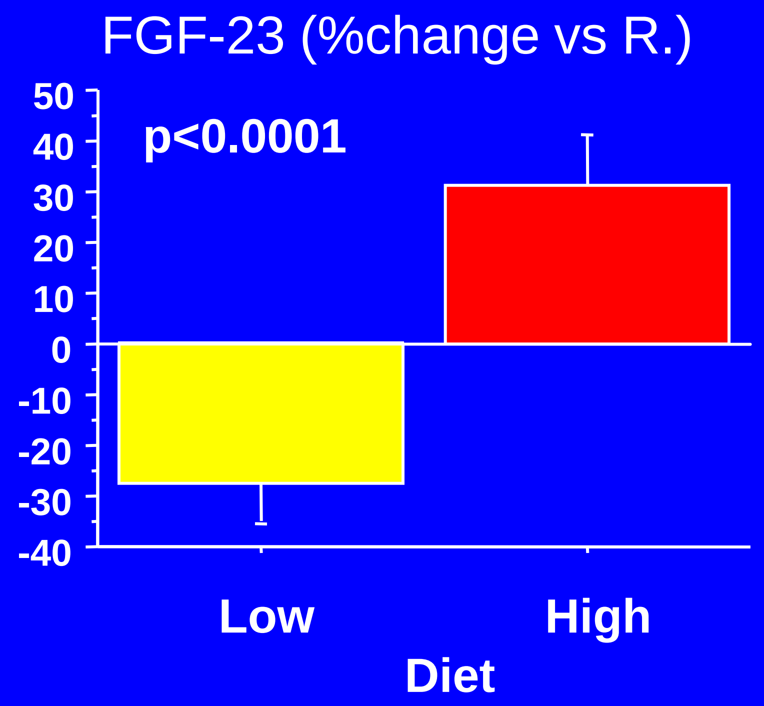
Geneva University Hospital

Switzerland

J Clin Endocrlinol Metab 2005; 90 1519-1524

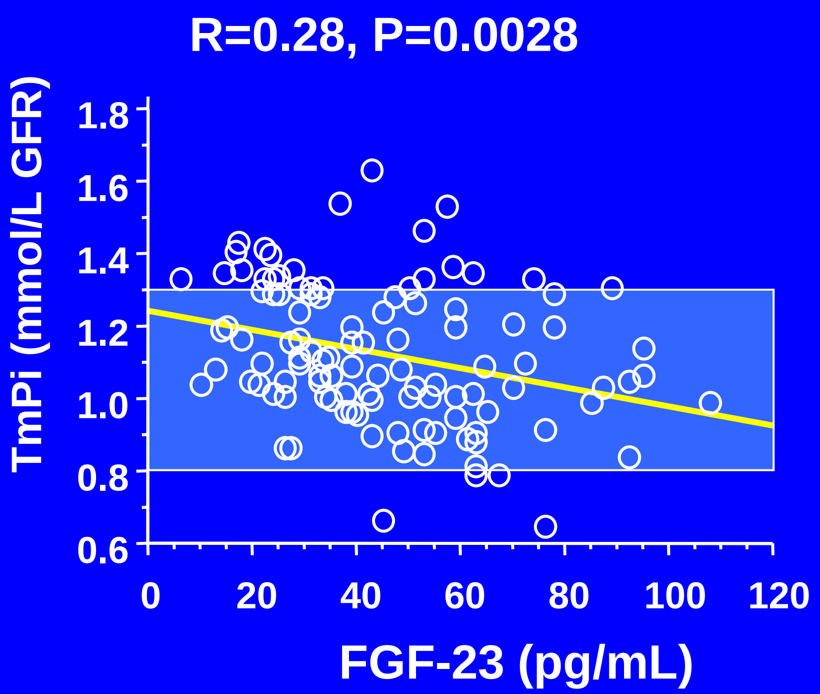
Results: FGF-23 and diet

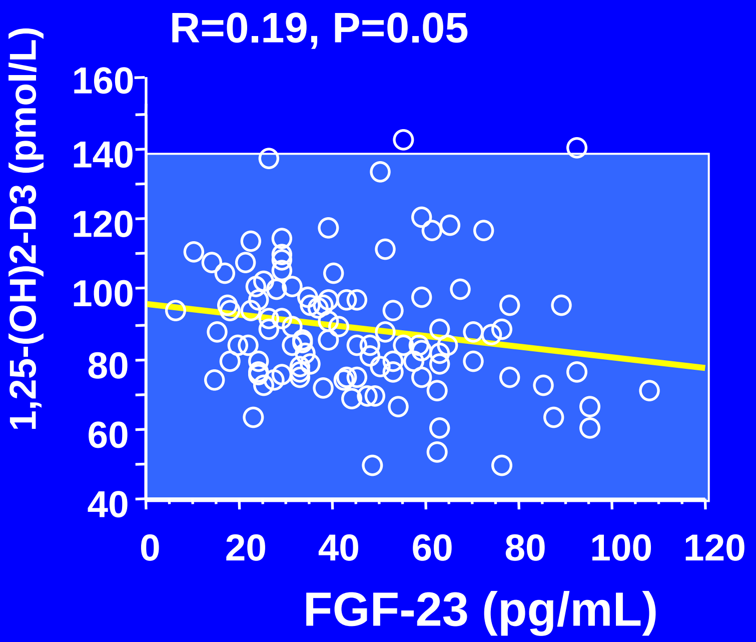




Ferrari et al. J Clin Endocrlinol Metab 2005; 90 1519-1524

FGF-23, PTH and tubular reabsorption of phosphate (TmPi)





Normal Range

Ferrari et al. J Clin Endocrlinol Metab 2005; 90 1519-1524

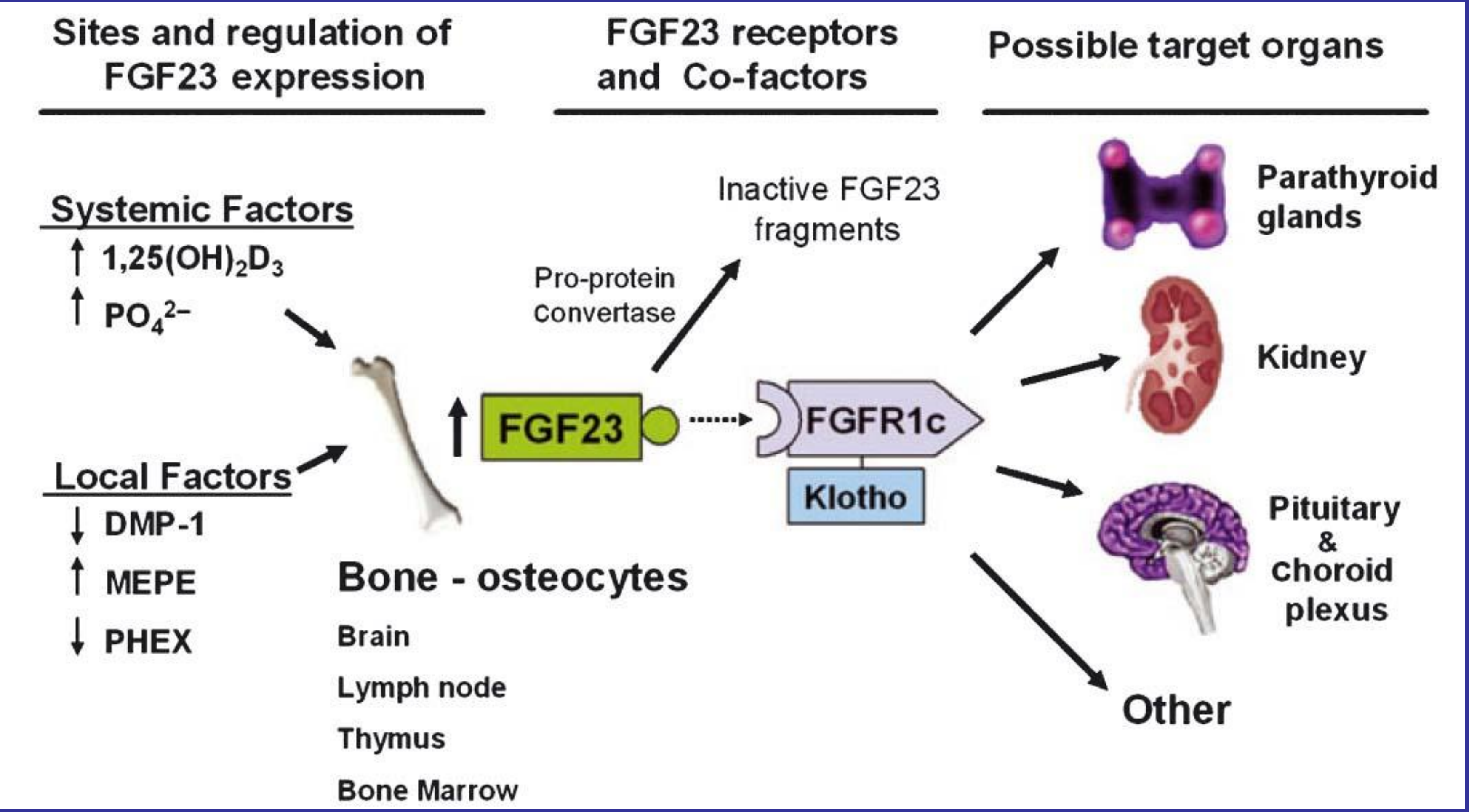


FIG. 2. The phosphaturic hormone FGF23 is predominately produced by osteocytes in bone and is regulated by $1,25(OH)_2D_3$ and phosphate as well as by Phex and extracellular matrix SIBLING proteins in bone. FGF23 targets FGFR1c/Klotho complexes that appear to be restricted to parathyroid glands, kidney, pituitary gland and choroid plexus. FGF23 inhibits sodium-dependent phosphate uptake and $1,25(OH)_2D_3$ production by the kidney. The effects of FGF23 on other potential target organs are not known.

Stubbs & Quarles Semin.Dial 2007

Greek Mythology
Life span controlled
by the 3 daughters of Zeus and Themis

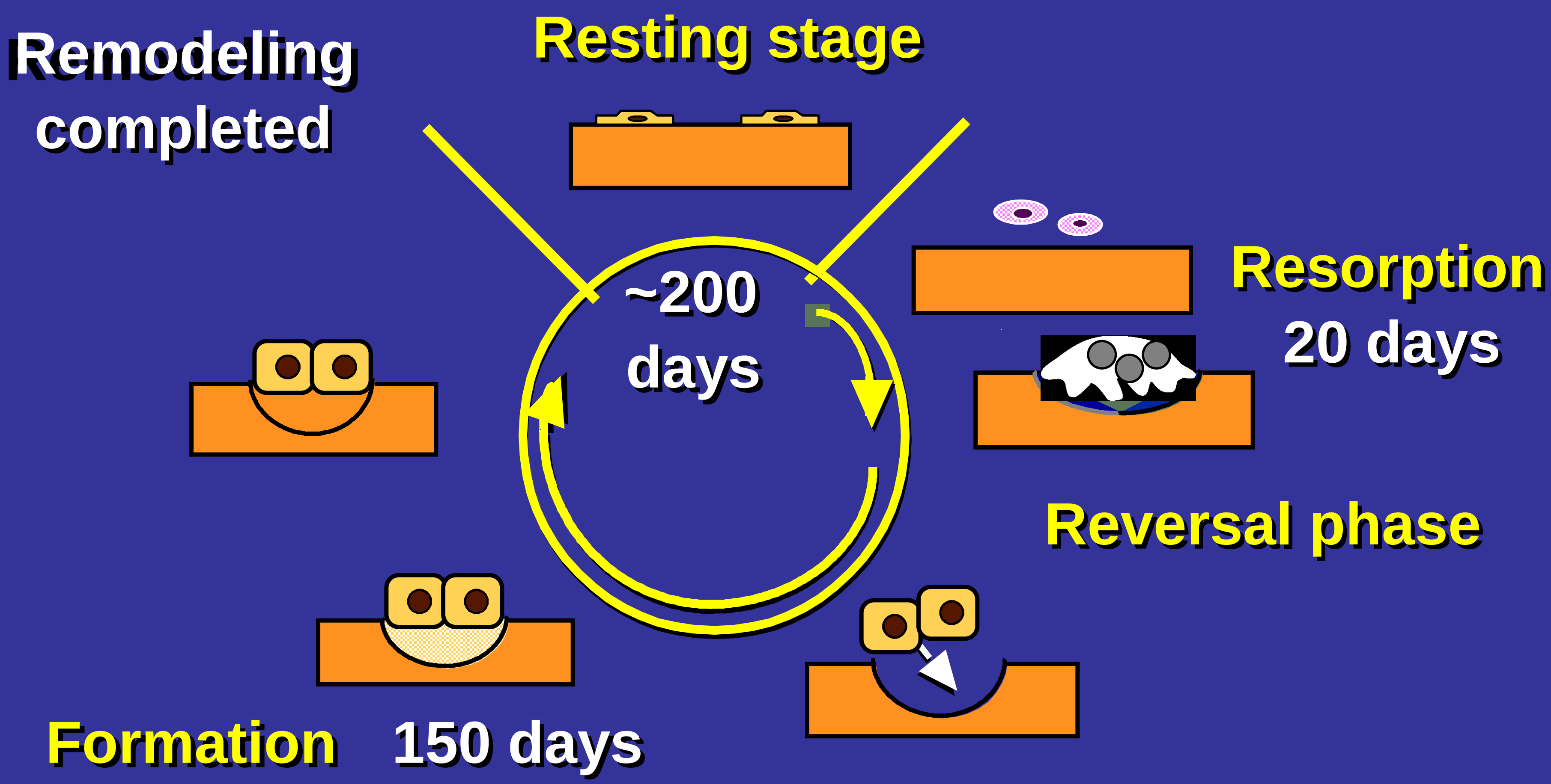
Klotho who spins the thread of life.

Lachesis who determines the span of life by measuring the length of thread.

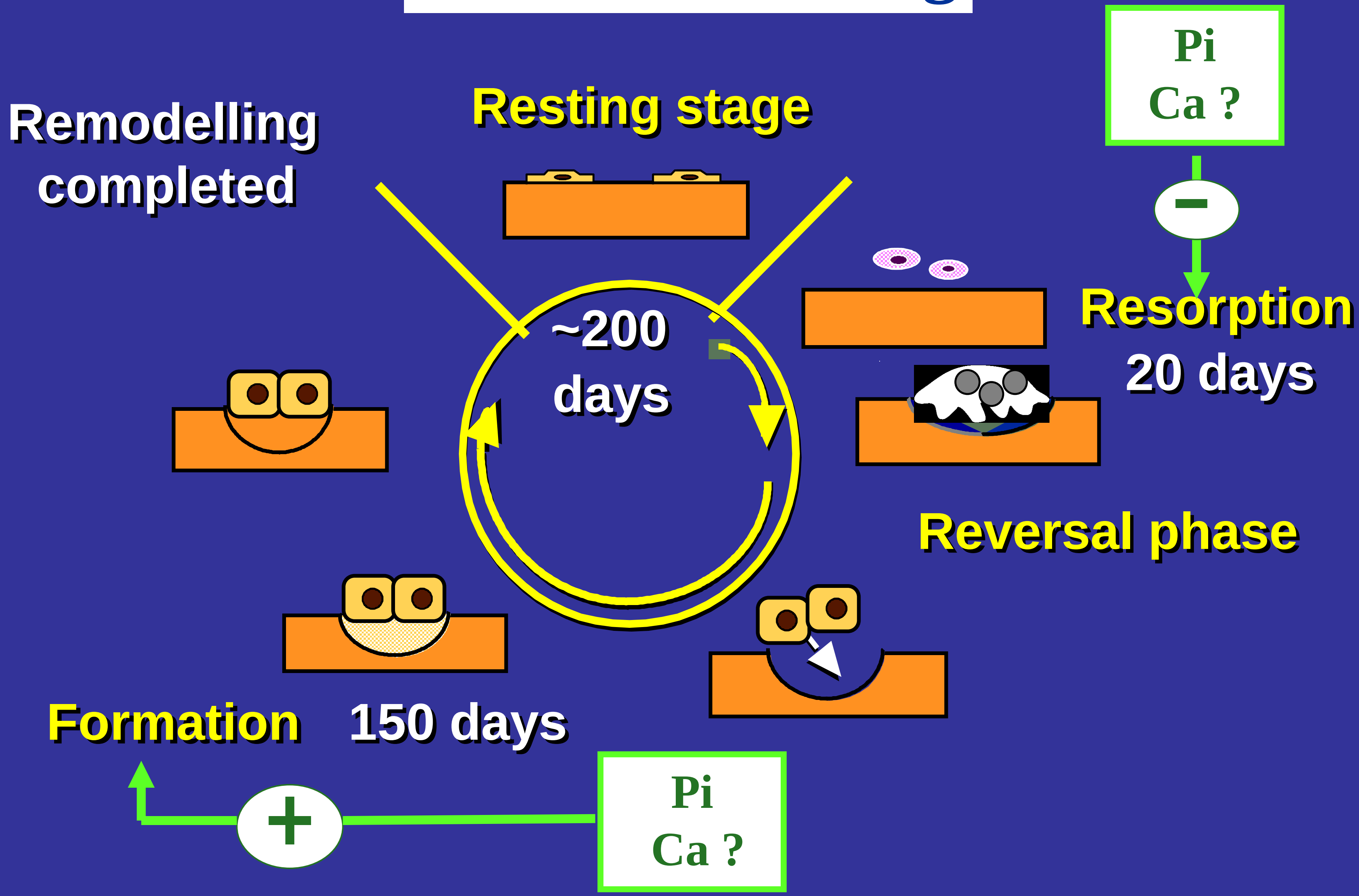
Athropos who cuts the string
to bring a life to an end.

Tibor DENGYEL Fantastique et mythologie Les trois Parques

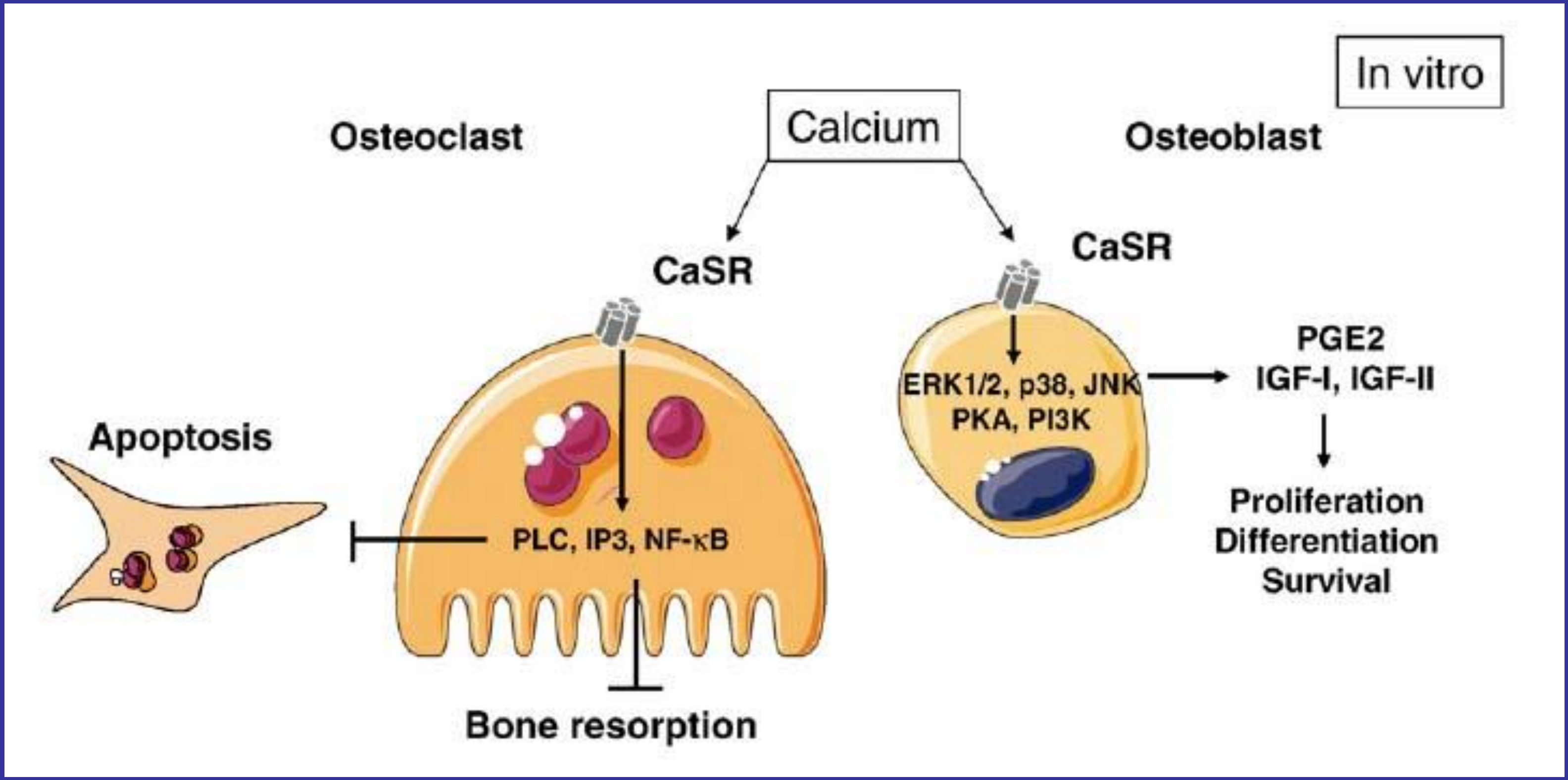
Bone Remodeling



Bone Remodeling



Interactions between Pi, Ca and Bone Cells



Marie P. Bone 46: 571-6. 2010

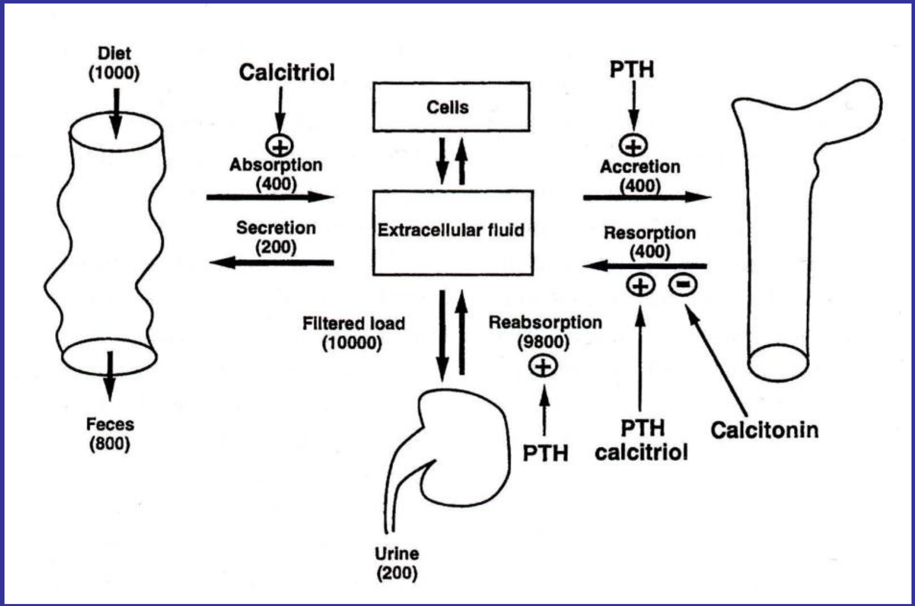
Ca Homeostasis: Main Fluxes & Regulators

Pi Homeostasis: Main Fluxes & Regulators

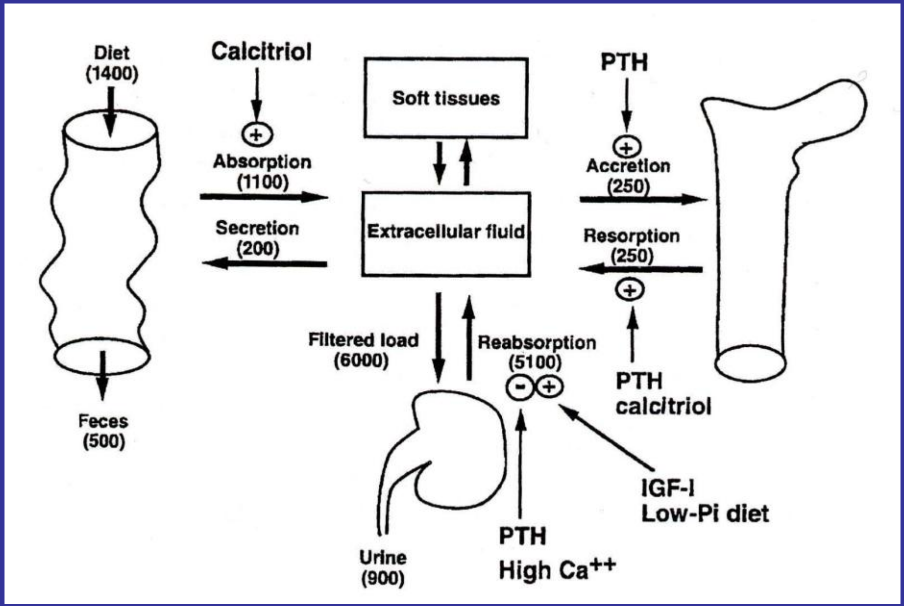
Distinct Extraskeletal Roles

Main Fluxes

Calcium



Phosphate



From Rizzoli & Bonjour. Physiology of Calcium and Phosphate Homeostasis. In: Dynamics of Bone and Cartilage Metabolism. Eds Seibel, Robins, Bilezikian. Academic Press, 2006

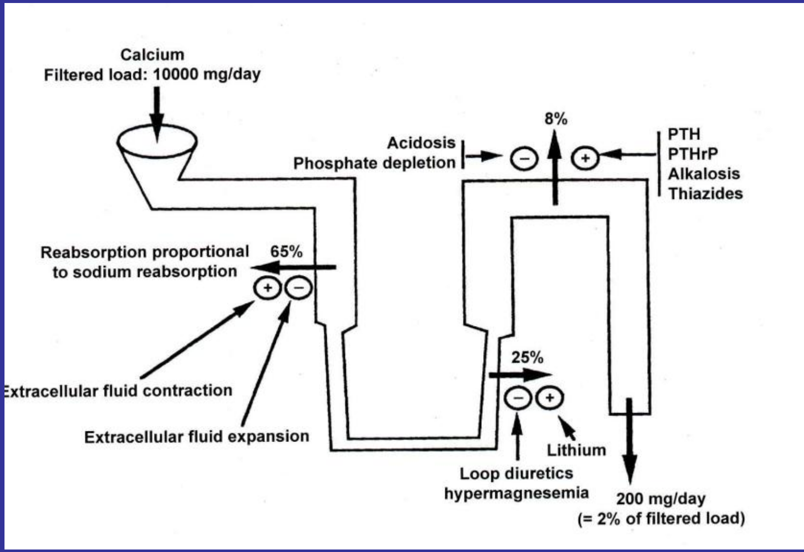
Essential Role of Renal Tubular Reabsorption in Ca and Pi Homeostasis

But Distinct Transporters
and
Distinct Regulators

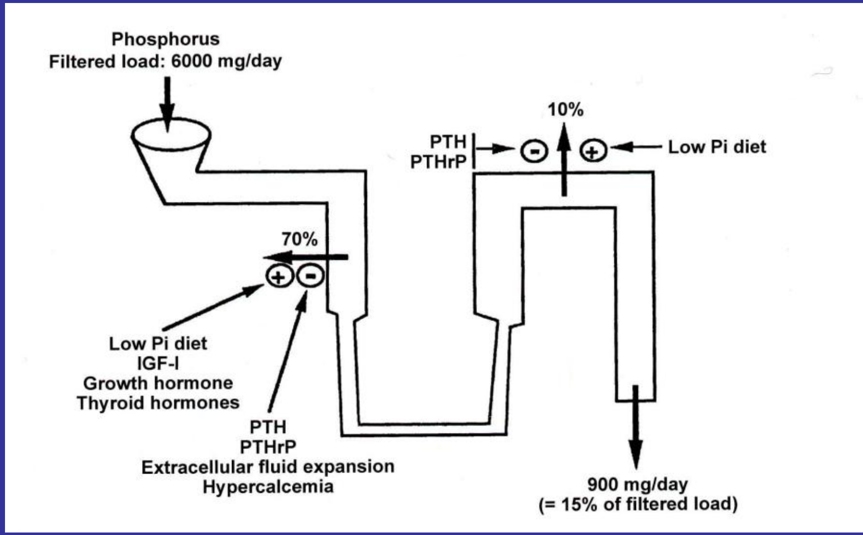
Ca Homeostasis: Main Fluxes & Regulators
Pi Homeostasis: Main Fluxes & Regulators
} Distinct Extraskeletal Roles

Renal Handling

Calcium



Phosphate

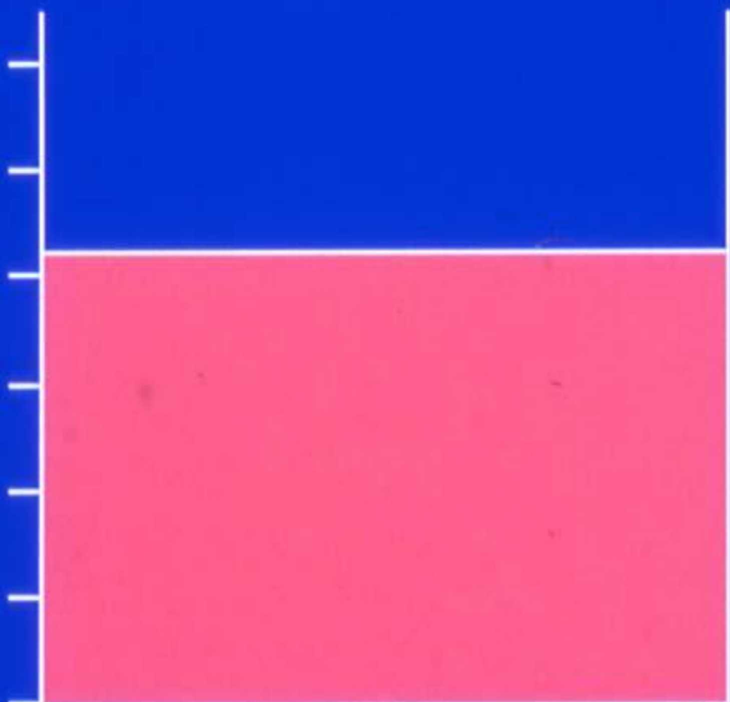


From Rizzoli & Bonjour. Physiology of Calcium and Phosphate Homeostasis. In: Dynamics of Bone and Cartilage Metabolism. Eds Seibel, Robins, Bilezikian. Academic Press, 2006

Extracellular concentration at steady state

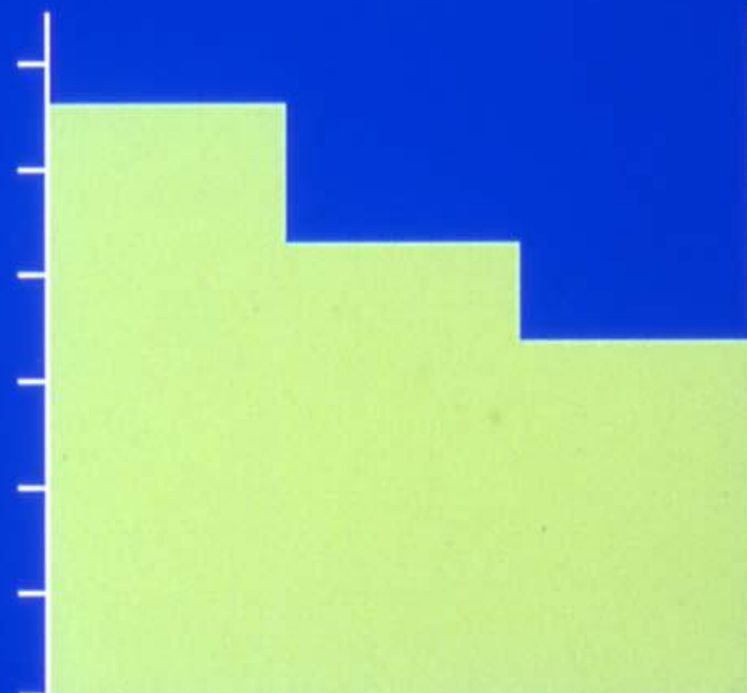
Ca^{++}

set at <u>one</u> level



Pi

set at <u>various</u> levels



Ca Homeostasis: Main Fluxes & Regulators

Pi Homeostasis: Main Fluxes & Regulators

Distinct Extraskeletal Roles

TABLE I. Physiological Roles of Calcium and Phosphate

	Calcium	Phosphate
Structural constituent	Hydroxyapatite (99% body calcium) Exchangeable pool (mineral storage)	Hydroxyapatite (85% body phosphorus) Nucleic acids Carbohydrates Lipids
Function	Intracellular signal transduction Cell adhesion Cell proliferation and differentiation Membrane permeability (neuromuscular excitability, muscle contraction, neurotransmission) Cytoskeleton (cell motility) Exo-/endosecretion Coagulation	Energy storage and delivery Intracellular signal transduction Enzyme activity Acid–base homeostasis

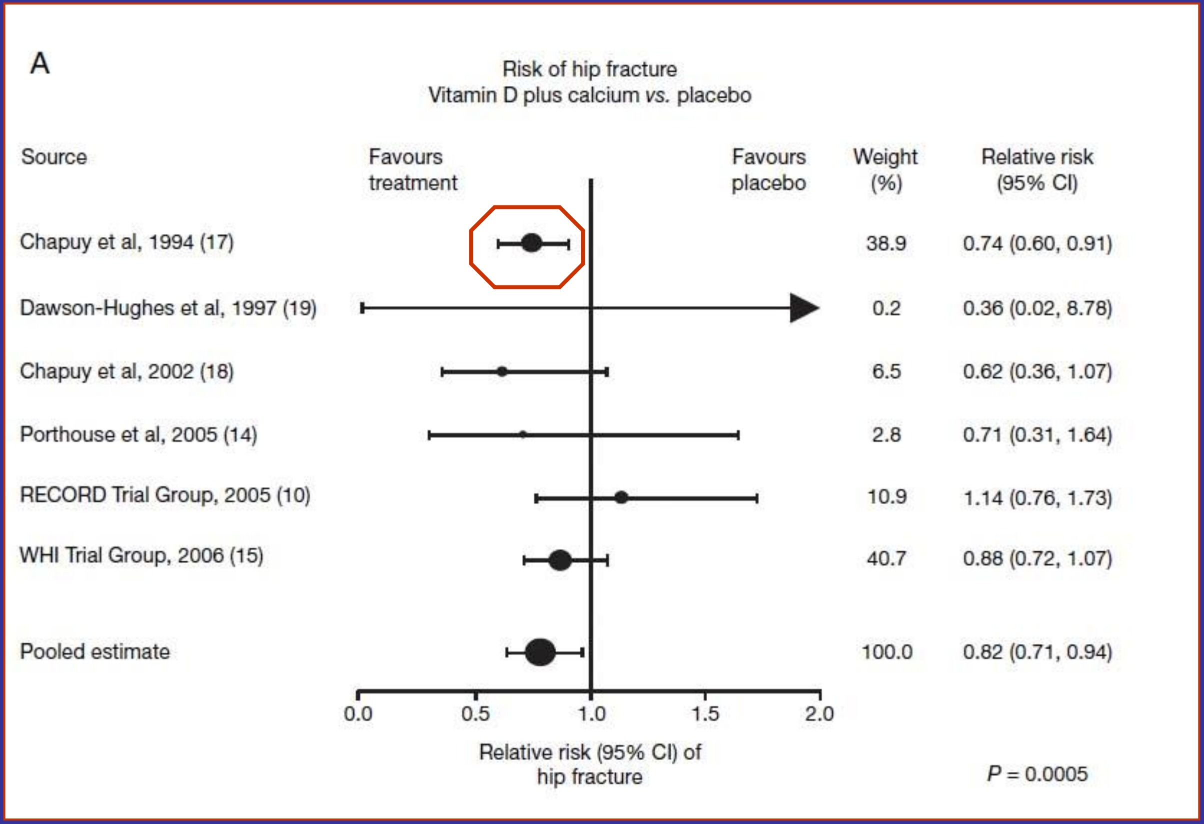
From Rizzoli & Bonjour. Physiology of Calcium and Phosphate Homeostasis. In: Dynamics of Bone and Cartilage Metabolism. Eds Seibel, Robins, Bilezikian. Academic Press, 2006

Calcium and Phosphate: A Duet of Ions Playing for Bone Health

Relative importance of Ca and Pi in Osteoporosis Management

Need for Additional Calcium to Reduce the Risk of Hip Fracture with Vitamin D Supplementation: Evidence from a Comparative Metaanalysis of Randomized Controlled Trials

Boonen JCEM 2007



Ca-Pi salt

Relative importance of Ca and Pi in Osteoporosis Management

Calcium Effects on Phosphorus Absorption: Implications for the Prevention and Co-Therapy of Osteoporosis

Robert P. Heaney, MD, FACN, and B. E. C. Nordin, MD

Phosphorus Nutrition and the Treatment of Osteoporosis

Robert P. Heaney, MD

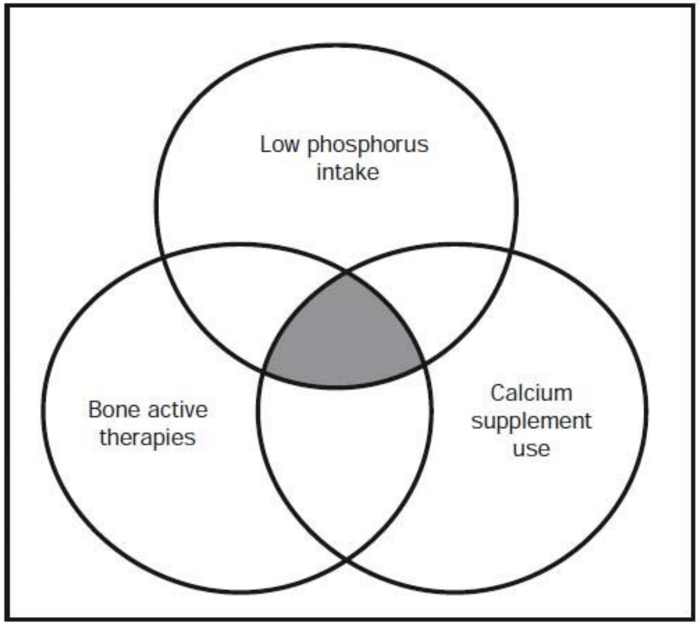


Figure 1. Portion of the elderly osteoporotic population most likely to be susceptible to insufficient phosphorus intake. Domain sizes are not drawn to scale.

Treating Osteoporosis with Pi

Fulfillment of Ca and Pi RDA by Foods vs. by Medication Preparations

Effect of calcium supplements on risk of myocardial infarction and cardiovascular events: meta-analysis

Mark J Bolland, senior research fellow,[1] Alison Avenell, clinical senior lecturer,[2] John A Baron, professor,[3] Andrew Grey, associate professor,[1] Graeme S MacLennan, senior research fellow,[2] Greg D Gamble, research fellow,[1] Ian R Reid, professor[1]

BJM 2010

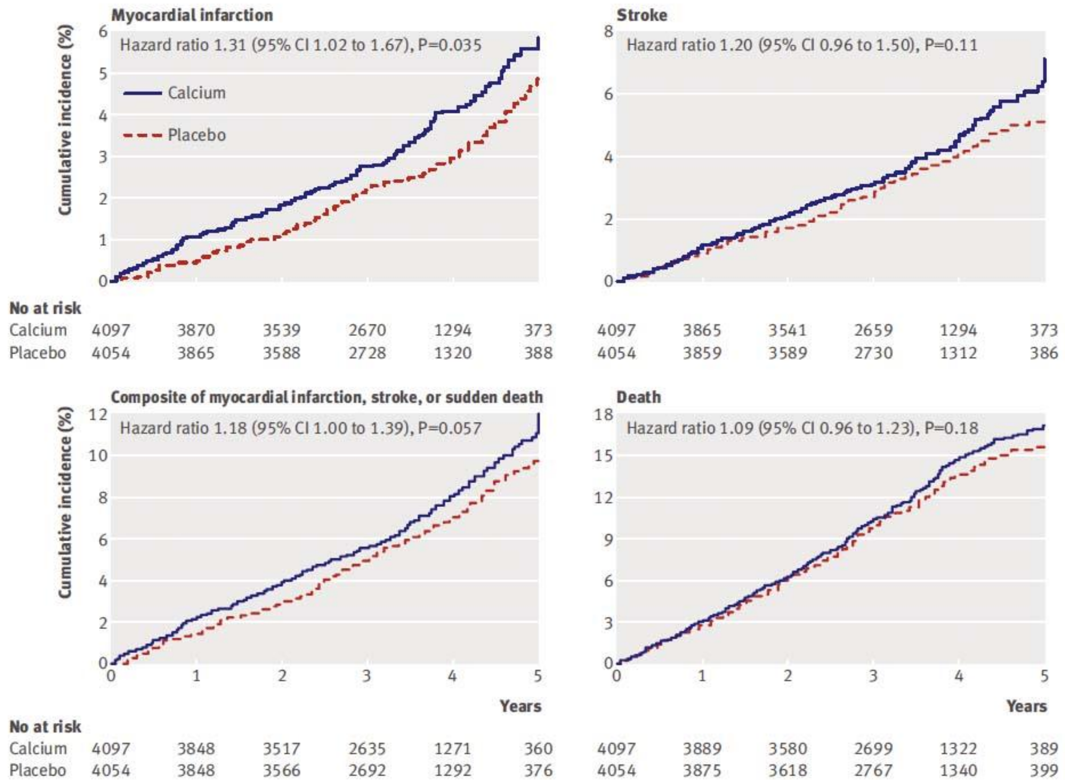


Fig 2 | Cumulative incidence of myocardial infarction, stroke, composite of myocardial infarction, stroke, or sudden death, and death by treatment allocation in five studies that contributed patient level data

Fulfillment of Ca and Pi RDA by Foods vs. by Medication Preparations

Effect of calcium supplements on risk of myocardial infarction and cardiovascular events: meta-analysis

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BJM 2010

"No association between myocardial events in individuals who use dietary calcium in dairy and other high calcium food to maintain adequate calcium intake. The reasons for these differences are also unknown but may involve a slower increase in serum calcium in individuals receiving high calcium-containing foods than in those using calcium supplements."

Comments from Jo Lorenzo
Scientific Web Blog ASBMR Editor.

Ca & Pi

Play Duet For Bone

Play Solo

For Other Vital Functions