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

Relative importance of Ca and Pi in Osteoporosis Management

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

Distinct Extraskeletal Roles
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
Bone Functions and Composition

Cortical, Compact Bone

Mineral: 60% mainly Ca-Pi

Organic Matrix: 30% mainly proteins

Water: 10%

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

Bone Functions and Composition

Bone Cells

- **Osteoclasts**: 1-2%
- **Osteoblasts**: 4-6%
- **Osteocytes**: 90-95%
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Bone Trajectory Throughout Life
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Ca/Pi Ratio in Bone Compared to Dairy Products

70 kg Human Adult

<table>
<thead>
<tr>
<th>Mass</th>
<th>% Whole Body</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ca: 1300 g</td>
<td>99</td>
</tr>
<tr>
<td>P: 700 g</td>
<td>80</td>
</tr>
</tbody>
</table>

Bone Crystal

Hydroxyapatite

$[\text{Ca}_{10}(\text{PO}_4)_6(\text{OH})_2]$
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MassCa/P Ratio in Bone Compared to Dairy Products

1.9-2.4

Human Milk

2.2
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MassCa/P Ratio in Bone Compared to Dairy Products

**Human Milk**: 1.9-2.4

**Cow Milk**: 2.2

**Ewe Milk**: 1.3

**Other Dairy Products**: 1.3
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Distinct Bone Pathologic Expression of Pi vs. Ca Dietary Restriction

Normal Ca-Pi Supply  Pi Restriction  Ca Restriction

Bone Matrix  Bone Mineral

Osteomalacia  Osteoporosis
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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
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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
1 & 2 Preosteoblasts
3 Osteoblasts
4 & 5 Osteoblastic Osteocytes (Preosteocytes)
6, 7 & 8 Osteocytes
Buried Alive: How Osteoblasts Become Osteocytes

Tamara A. Franz-Odendaal,\textsuperscript{1,}\textasteriskcentered Brian K. Hall,\textsuperscript{1} and P. Eckhard Witten\textsuperscript{1,2,}\textasteriskcentered
Buried Alive: How Osteoblasts Become Osteocytes

Tamara A. Franz-Odendaal,¹* Brian K. Hall,¹ and P. Eckhard Witten¹,²*

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
Back to the Old Seventies
and

Physiology and Pathophysiology

The Concept of a Putative
Bone-Kidney Link in Pi Homeostasis
Is there a bone-kidney link in the homeostasis of inorganic phosphate (Pi)?

Pharmacological Inhibition of Bone Mineralization

FGF 23 ?
- Renal Pi Reabsorption

1,25-VitD
- Intestinal Ca-Pi Absorption
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 Endocrinol Metab 2005; 90 1519-1524
Results: FGF-23 and diet

FGF-23 (pg/mL)

FGF-23 (%change vs R.)

P=0.0004

p<0.0001

Ferrari et al. J Clin Endocrinol Metab 2005; 90 1519-1524
FGF-23, PTH and tubular reabsorption of phosphate (TmPi)

- FGF-23 (pg/mL) vs. TmPi (mmol/L GFR)
  - R=0.28, P=0.0028

- 1,25-(OH)2-D3 (pmol/L) vs. FGF-23 (pg/mL)
  - R=0.19, P=0.05

Ferrari et al. J Clin Endocrinol 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.
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.
Remodeling completed

Resting stage

Formation 150 days

Resorption 20 days

Reversal phase

Bone Remodeling

~200 days
Bone Remodeling

Remodelling completed

Resting stage

~200 days

Resorption

20 days

Reversal phase

Formation

150 days

Pi Ca ?

Pi Ca ?
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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

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

Renal Handling

Calcium

Phosphate

Distinct Extraskeletal Roles

Extracellular concentration at steady state

$\text{Ca}^{++}$
set at one level

$\text{Pi}$
set at various levels
### TABLE I.  Physiological Roles of Calcium and Phosphate

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

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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

A

Risk of hip fracture
Vitamin D plus calcium vs. placebo

<table>
<thead>
<tr>
<th>Source</th>
<th>Favours treatment</th>
<th>Favours placebo</th>
<th>Weight (%)</th>
<th>Relative risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chapuy et al, 1994 (17)</td>
<td></td>
<td></td>
<td>38.9</td>
<td>0.74 (0.60, 0.91)</td>
</tr>
<tr>
<td>Dawson-Hughes et al, 1997 (19)</td>
<td></td>
<td></td>
<td>0.2</td>
<td>0.36 (0.02, 8.76)</td>
</tr>
<tr>
<td>Chapuy et al, 2002 (18)</td>
<td></td>
<td></td>
<td>6.5</td>
<td>0.62 (0.36, 1.07)</td>
</tr>
<tr>
<td>Porthouse et al, 2005 (14)</td>
<td></td>
<td></td>
<td>2.8</td>
<td>0.71 (0.31, 1.64)</td>
</tr>
<tr>
<td>RECORD Trial Group, 2005 (10)</td>
<td></td>
<td></td>
<td>10.9</td>
<td>1.14 (0.76, 1.73)</td>
</tr>
<tr>
<td>WHI Trial Group, 2006 (15)</td>
<td></td>
<td></td>
<td>40.7</td>
<td>0.88 (0.72, 1.07)</td>
</tr>
<tr>
<td>Pooled estimate</td>
<td></td>
<td></td>
<td>100.0</td>
<td>0.82 (0.71, 0.94)</td>
</tr>
</tbody>
</table>

Relative risk (95% CI) of hip fracture

P = 0.0005

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.
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;4 Graeme S MacLennan, senior research fellow;5 Greg D Gamble, research fellow;6 Ian R Reid, professor7

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
“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