Fra' Angelico, Annunciazione (1430-32) Museo del Prado, Madrid

Azioni generali del calcio

- **Extracellulari**
  - **Mineralizzazione osso**
  - **Coagulazione**
  - **Eccitabilita' neuromuscolare**
- **Intracellulari**
  - **Attivazione neuronale**
  - **Contrazione muscolare**
  - **Secrezione ormoni**
  - **Secondo messaggero per ormoni e fattori di crescita**
  - **Regolazione transcrizione genica ed attivita' metaboliche**

Sintomi e Segni dell'ipercalcemia (I)

1) Interessamento del Sistema Nervoso Centrale
   - Letargia
   - Depressione
   - Stupor
   - Coma

2) Interessamento Neuromuscolare
   - Astenia
   - Miopatia prossimale
   - Ipotrofia muscolare

3) Interessamento cardiovascolare
   - Ipertensione
   - Bradicardia
   - Potenziamento effetti tossici della digitale

Sintomi e Segni dell'ipercalcemia (II)

4) Interessamento renale
   - Poliuria
   - Nefrolitiasi
   - Nefrocalcinosi

5) Interessamento gastro-intestinale
   - Nausea, Vomito
   - Stipsi
   - Dispepsia
   - Ulcera peptica
   - Pancreatite

6) Calcificazioni tessuti molli
   - Prurito
   - Condrocalcinosi
   - Nefrocalcinosi

Sintomi e Segni dell'ipocalcemia (I)

1) Aumentata eccitbilità neuromuscolare
   - Tetania latente (segno di Chvostek, segno di Trousseau, ipereflessia osteotendinea)
   - Tetania conclamata (parestesie, spasmi mscolari, convulsioni)

2) Interessamento del SNC
   - Turbe mentali (ansia, depressione, psicosi)
   - calcificazioni dei nuclei della base associati talora a disturbi extrapiramidali
   - papilledema e ipertensione endocranica

3) Cataratta

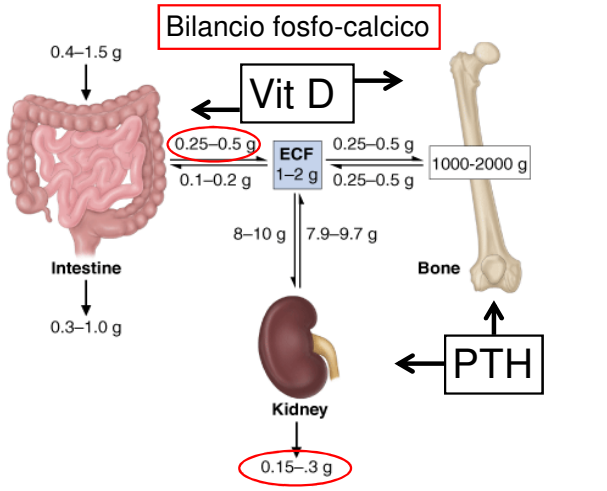
Sintomi e Segni dell'ipocalcemia (II)

4) Disturbi trofici
   - cute
   - apparato pilifero
   - unghie
   - denti

5) Allungamento del tratto QT

6) Insufficienza cardiaca congestizia

7) Sindrome da malassorbimento



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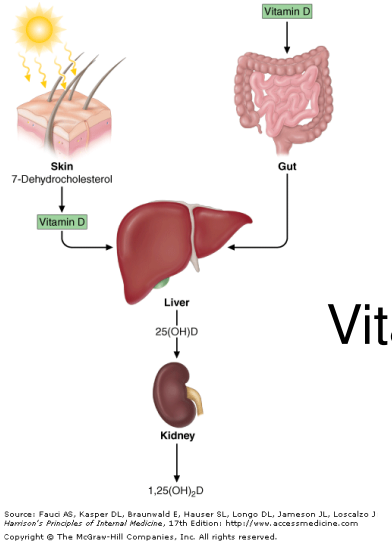
ECF
1–2 g

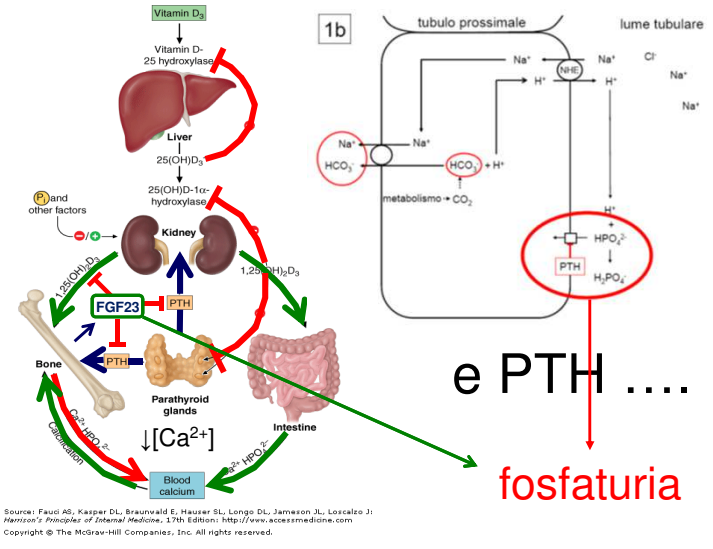
2.2-2.6 mMoli x L^{-1} (totale)

1.2 mM libero (50%)

0.24 mMoli x L^{-1} (10%) legato a Pi e bicarbonato ⟺ 0.96 mMoli x L^{-1} (40%) legato a proteine

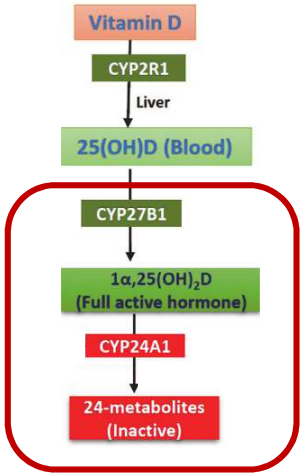


Vitamina D ….



e PTH ….

fosfaturia



Rene

Hormonal regulation of biomineralization

Andrew Arnold[1], Elaine Dennison[2], Christopher S. Kovacs[3], Michael Mannstadt[4], René Rizzoli[5], Maria Luisa Brandi[6], Bart Clarke[7] and Rajesh V. Thakker[8]

Abstract | Biomineralization is the process by which organisms produce mineralized tissues. This crucial process makes possible the rigidity and flexibility that the skeleton needs for ambulation and protection of vital organs, and the hardness that teeth require to tear and grind food. The skeleton also serves as a source of mineral in times of short supply, and the intestines absorb and the kidneys reclaim or excrete minerals as needed. This Review focuses on physiological and pathological aspects of the hormonal regulation of biomineralization. We discuss the roles of calcium and inorganic phosphate, dietary intake of minerals and the delicate balance between activators and inhibitors of mineralization. We also highlight the importance of tight regulation of serum concentrations of calcium and phosphate, and the major regulators of biomineralization: parathyroid hormone (PTH), the vitamin D system, vitamin K, fibroblast growth factor 23 (FGF23) and phosphatase enzymes. Finally, we summarize how developmental stresses in the fetus and neonate, and in the mother during pregnancy and lactation, invoke alternative hormonal regulatory pathways to control mineral delivery, skeletal metabolism and biomineralization.

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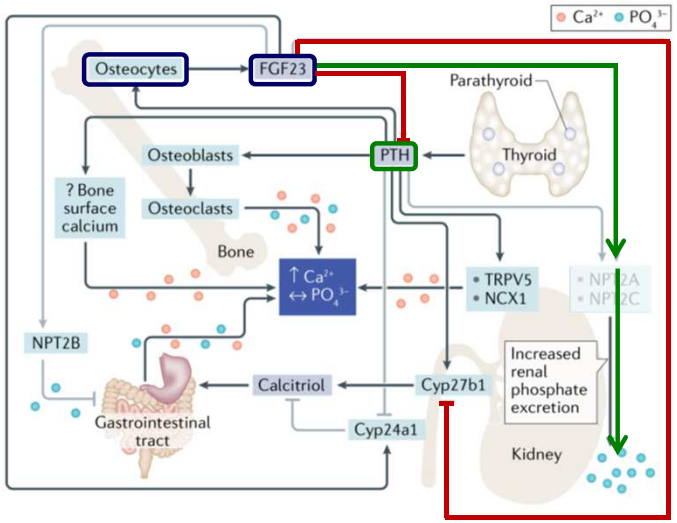
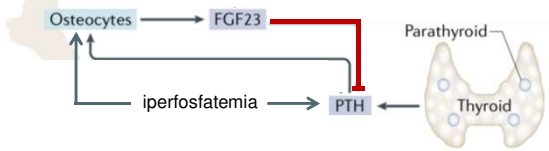


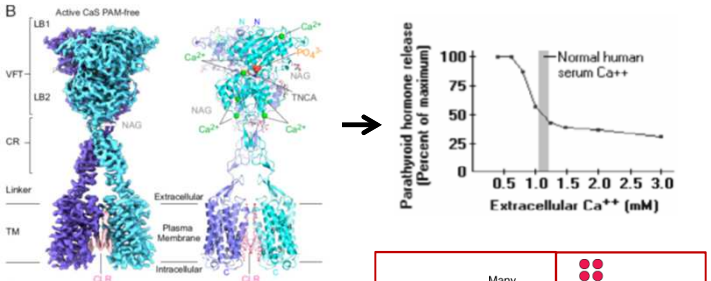
Fig. 1 | **Regulation of calcium and phosphate economy and bone mass.** The secretion of parathyroid hormone (PTH) from the parathyroid glands increases in response to low serum concentrations of calcium (Ca^{2+}). Within bone cells, PTH stimulates osteoblasts to form bone, indirectly stimulates osteoclasts to resorb bone and bring calcium and phosphate (PO_4^{3-}) into the circulation, and acts on osteocytes to stimulate the release of fibroblast growth factor 23 (FGF23). Within kidney tubules, PTH increases reabsorption of calcium and renal excretion of phosphate, and FGF23 also stimulates renal phosphate excretion. FGF23 acts indirectly on the intestines by controlling the level of calcitriol, but might also have direct actions to regulate the expression of the sodium-dependent phosphate transport protein 2B (NPT2B). Within intestines, calcitriol increases intestinal calcium and phosphate absorption. The integration of these regulators includes that PTH increases the release of FGF23 and increases calcitriol levels, whereas FGF23 has opposing effects to inhibit PTH and decrease calcitriol. The central, dark-blue box indicates the circulating or blood concentrations of calcium and phosphate. The question mark indicates an unclear process. Black arrows indicate pathways with net stimulatory actions whereas grey arrows are pathways with net inhibitory action. Flat arrowheads indicate inhibitory actions. Adapted from REF.[172], Springer Nature Limited.

Carenza di ferro
Eritropoietina
Citochine infiammatorie



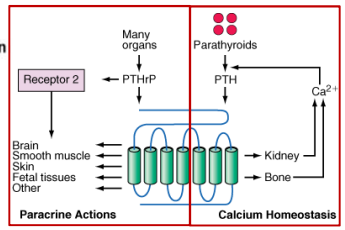
The primary hormonal regulator of serum phosphate levels is the phosphaturic hormone bone-derived FGF23 (REF.[39]). PTH, which is primarily a calciotropic hormone, also regulates phosphate homeostasis. In the kidney, PTH and FGF23 lead to the relatively rapid removal of NPT2A and NPT2C from the brush border membrane (BBM) of the proximal tubule. Endocytosis and lysosomal degradation of these transporters results in renal phosphate wasting and a decrease in blood phosphate levels.

Of note, PTH and FGF23 have opposite effects on vitamin D metabolism. PTH increases the production of calcitriol, which increases the intestinal absorption of calcium (discussed in detail later) and, to a lesser degree, phosphate. By contrast, FGF23 inhibits production of calcitriol. The release of both PTH and FGF23 are stimulated by hyperphosphataemia; FGF23 is also stimulated by iron deficiency, erythropoietin and inflammatory cytokines, and PTH mainly by hypocalcaemia[40–42].



Symmetric activation and modulation of the human calcium-sensing receptor

Park et al **PNAS** 2021 Vol. 118 No. 51 e2115849118



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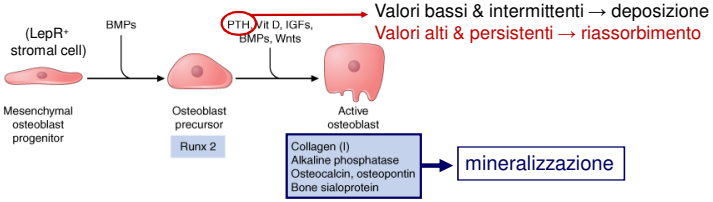
Osteoblasti & osteoclasti - regolazione



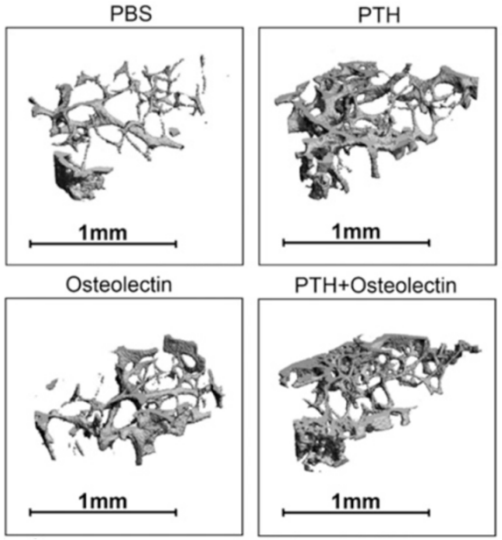
PNAS 2021 Vol. 118 No. 25 e2026176118

The effect of parathyroid hormone on osteogenesis is mediated partly by osteolectin

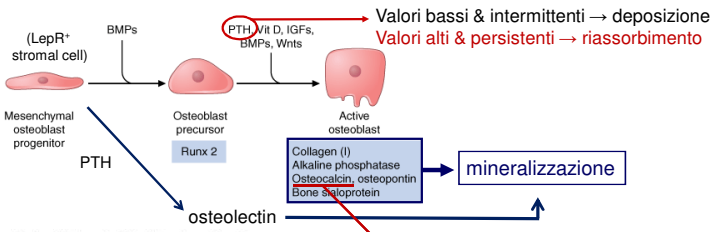
Jingzhu Zhang[a], Adi Cohen[b], Bo Shen[a], Liming Du[a], Alpaslan Tasdogan[a], Zhiyu Zhao[a], Elizabeth J. Shane[b], and Sean J. Morrison[a,c,d,1]

[a]Children's Research Institute, University of Texas Southwestern Medical Center, Dallas, TX 75235; [b]Department of Medicine, Vagelos College of Physicians & Surgeons, Columbia University, New York, NY 10032; [c]HHMI, University of Texas Southwestern Medical Center, Dallas, TX 75235; and [d]Department of Pediatrics, University of Texas Southwestern Medical Center, Dallas, TX 75235

We previously described a new osteogenic growth factor, osteolectin/Clec11a, which is required for the maintenance of skeletal bone mass during adulthood. Osteolectin binds to Integrin α11 (Itga11), promoting Wnt pathway activation and osteogenic differentiation by leptin receptor+ (LepR+) stromal cells in the bone marrow. Parathyroid hormone (PTH) and sclerostin inhibitor (SOSTi) are bone anabolic agents that are administered to patients with osteoporosis. Here we tested whether osteolectin mediates the effects of PTH or SOSTi on bone formation. We discovered that PTH promoted *Osteolectin* expression by bone marrow stromal cells within hours of administration and that PTH treatment increased serum osteolectin levels in mice and humans. *Osteolectin* deficiency in mice attenuated Wnt pathway activation by PTH in bone marrow stromal cells and reduced the osteogenic response to PTH in vitro and in vivo. In contrast, SOSTi did not affect serum osteolectin levels and osteolectin was not required for SOSTi-induced bone formation. Combined administration of osteolectin and PTH, but not osteolectin and SOSTi, additively increased bone volume. PTH thus promotes osteolectin expression and osteolectin mediates part of the effect of PTH on bone formation.



Osteoblasti & osteoclasti - regolazione

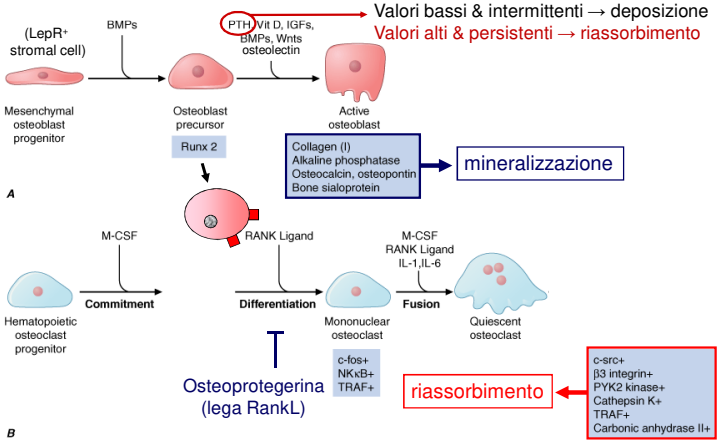


Role of vitamin K in biomineralization

There are two main species of vitamin K: phylloquinones (vitamin K1), which are found in green leafy vegetables; and menaquinones (vitamin K2), which are found in fermented foods. Both are cofactors for a post-translational carboxyl moiety that is added on to protein-bound glutamate residues, through a mechanism called γ-carboxylation[86]. The γ-carboxylation of the glutamate residues (that is, carboxyglutamic acid or Gla residues) is necessary for prothrombin activity, by providing a calcium-binding site involved in the coagulation cascade. However, at least 17 other proteins contain vitamin K-dependent Gla residues, among them osteocalcin[86].

Osteocalcin is the most abundant noncollagenous component in the mineralized matrix of bone. The presence of three Gla residues enables post-translational γ-carboxylation at positions 17, 21 and 24. Calcification is inhibited by the fully carboxylated form of osteocalcin[87]. By contrast, the undercarboxylated form of osteocalcin seems to regulate energy metabolism and reproductive function[87]. Studies of osteocalcin-deficient mice models, which display high bone mineral content, show that osteocalcin influences hydroxyapatite crystal growth and structure[86].

Osteoblasti & osteoclasti - regolazione



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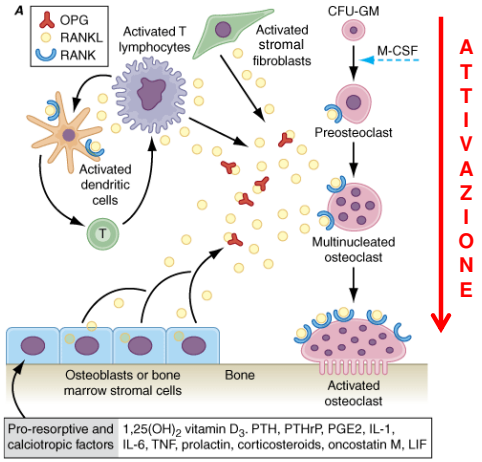

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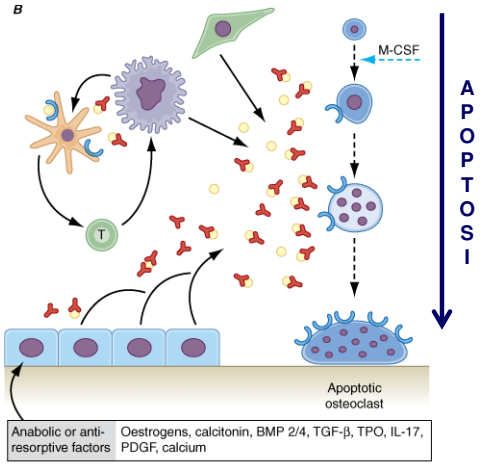

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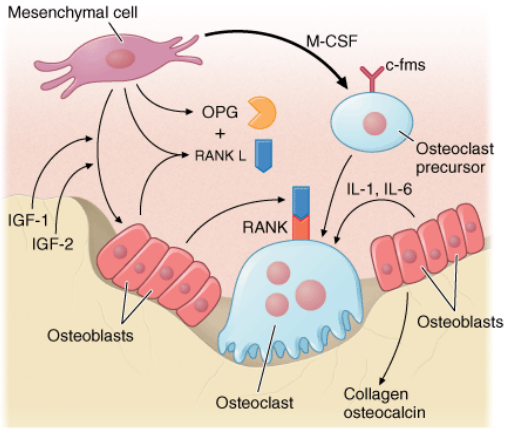

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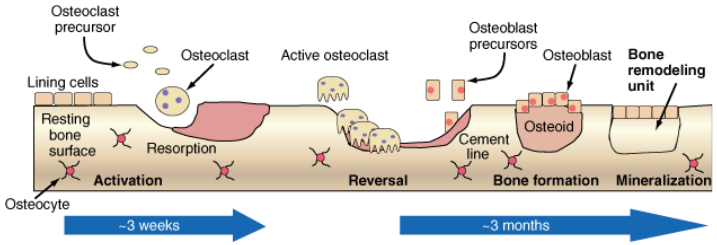
Osteoblasti & osteoclasti – rimodellamento osseo



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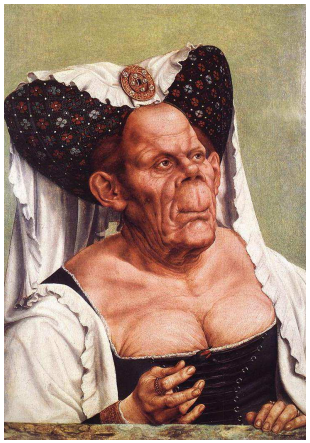
Paget's disease in a painting by Quinten Metsys (Massys)

J Dequeker

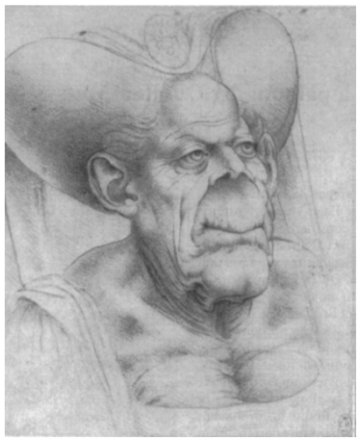
Arthritis and Metabolic Bone Disease Research Unit, University Hospital KU Leuven, 3041 Pellenberg, Belgium
J Dequeker, MD, *professor*

Br Med J 1989;**299**:1579-81

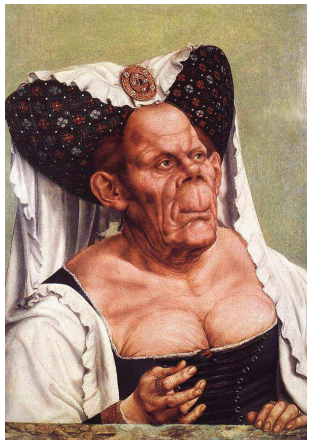
Naiken in 1971 and Baker in 1973 suggested that Beethoven was affected by Paget's disease, which may have been responsible for his deafness.



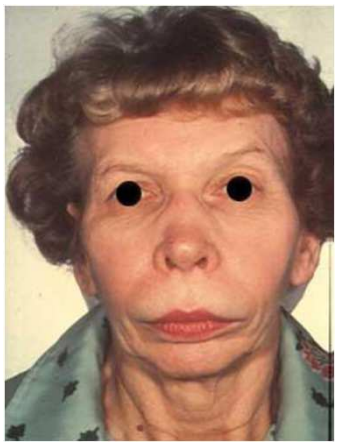
Quentin Metsys (1513)
Vecchia grottesca



Disegno di Leonardo da Vinci



Quentin Metsys (1513)
Vecchia grottesca



Malattia di Paget

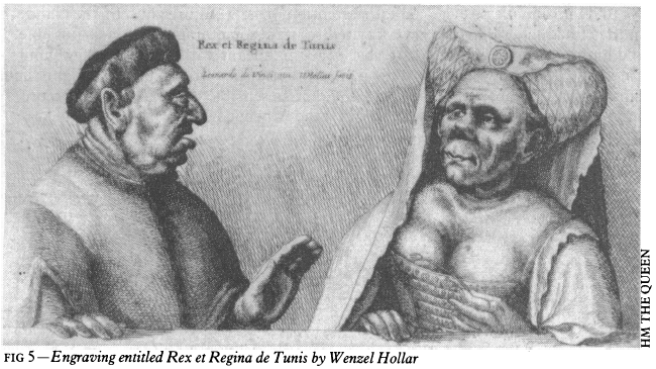


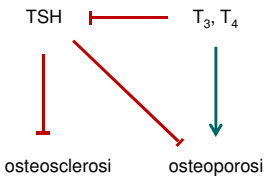
FIG 5—*Engraving entitled Rex et Regina de Tunis by Wenzel Hollar*

John Tenniel, illustration of the Duchess from *Alice in Wonderland*, 1869

TSH Is a Negative Regulator of Skeletal Remodeling

Etsuko Abe,[1,2] Russell C. Marians,[1] Wanqin Yu,[1,2]
Xue-Bin Wu,[1,2] Takao Ando,[1] Yanan Li,[3]
Jameel Iqbal,[1,2] Leslie Eldeiry,[1,2]
Gopalan Rajendren,[1,2] Harry C. Blair,[3,4]
Terry F. Davies,[1] and Mone Zaidi[1,2]

Cell, Vol. 115, 151–162, October 17, 2003

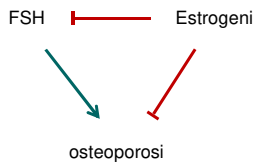


The established function of thyroid stimulating hormone (TSH) is to promote thyroid follicle development and hormone secretion. The osteoporosis associated with hyperthyroidism is traditionally viewed as a secondary consequence of altered thyroid function. We provide evidence for direct effects of TSH on both components of skeletal remodeling, osteoblastic bone formation, and osteoclastic bone resorption, mediated via the TSH receptor (TSHR) found on osteoblast and osteoclast precursors. Even a 50% reduction in TSHR expression produces profound osteoporosis (bone loss) together with focal osteosclerosis (localized bone formation). TSH inhibits osteoclast formation and survival by attenuating JNK/c-*jun* and NFκB signaling triggered in response to RANK-L and TNFα. TSH also inhibits osteoblast differentiation and type 1 collagen expression in a *Runx-2*- and osterix-independent manner by downregulating Wnt (LRP-5) and VEGF (Flk) signaling. These studies define a role for TSH as a single molecular switch in the independent control of both bone formation and resorption.

FSH Directly Regulates Bone Mass

Li Sun,[1] Yuanzhen Peng,[1] Allison C. Sharrow,[2,3] Jameel Iqbal,[1] Zhiyuan Zhang,[1] Dionysios J. Papachristou,[2,3] Samir Zaidi,[1] Ling-Ling Zhu,[1] Beatrice B. Yaroslavskiy,[2,3] Hang Zhou,[1] Alberta Zallone,[4] M. Ram Sairam,[5] T. Rajendra Kumar,[6] Wei Bo,[7] Jonathan Braun,[7] Luis Cardoso-Landa,[1] Mitchell B. Schaffler,[1] Baljit S. Moonga,[1] Harry C. Blair,[2,3,*] and Mone Zaidi[1,*]
[1] Mount Sinai Bone Program, Department of Medicine and Department of Orthopedics, Mount Sinai School of Medicine, New York, NY 10029, USA
[2] Departments of Pathology and Cell Biology, University of Pittsburgh, Pittsburgh, PA 15261, USA
[3] VA Medical Center, Pittsburgh, PA 15261, USA
[4] Department of Anatomy and Histology, University of Bari, 70124 Bari, Italy
[5] Clinical Research Institute of Montreal, Montreal, QC H2W 1R7, Canada
[6] Department of Molecular and Integrative Physiology, University of Kansas, Kansas City, KS 66160, USA
[7] Department of Pathology, University of California, Los Angeles, Los Angeles, CA 90095, USA
*Contact: hcblair@imap.upitt.edu (H.C.B.); mone.zaidi@mssm.edu (M.Z.)
DOI 10.1016/j.cell.2006.01.051

Cell *125*, 247–260, April 21, 2006



Postmenopausal osteoporosis, a global public health problem, has for decades been attributed solely to declining estrogen levels. Although FSH levels rise sharply in parallel, a direct effect of FSH on the skeleton has never been explored. We show that FSH is required for hypogonadal bone loss. Neither FSHβ nor FSH receptor (FSHR) null mice have bone loss despite severe hypogonadism. Bone mass is increased and osteoclastic resorption is decreased in haploin-sufficient $FSH\beta^{+/-}$ mice with normal ovarian function, suggesting that the skeletal action of FSH is estrogen independent. Osteoclasts and their precursors possess $G_{i2\alpha}$-coupled FSHRs that activate MEK/Erk, NF-κB, and Akt to result in enhanced osteoclast formation and function. We suggest that high circulating FSH causes hypogonadal bone loss.

Cell *125*, 247–260, April 21, 2006

REVIEW

FSH-metabolic circuitry and menopause

Charit Taneja, Sakshi Gera, Se-Min Kim, Jameel Iqbal, Tony Yuen and **Mone Zaidi**
The Mount Sinai Bone Program, Department of Medicine, Icahn School of Medicine at Mount Sinai, New York, New York, USA
Correspondence should be addressed to C Taneja: charit.taneja@mountsinai.org

Abstract

FSH has a primary function in procreation, wherein it induces estrogen production in females and regulates spermatogenesis in males. However, in line with our discoveries over the past decade of non-unitary functions of pituitary hormones, we and others have described *hitherto* uncharacterized functions of FSH. Through high-affinity receptors, some of which are variants of the ovarian FSH receptor (FSHR), FSH regulates bone mass, adipose tissue function, energy metabolism, and cholesterol production in both sexes. These newly described actions of FSH may indeed be relevant to the pathogenesis of bone loss, dysregulated energy homeostasis, and disordered lipid metabolism that accompany the menopause in females and aging in both genders. We are therefore excited about the possibility of modulating circulating FSH levels toward a therapeutic benefit for a host of age-associated diseases, including osteoporosis, obesity and dyslipidemia, among other future possibilities.

Key Words
- FSH
- menopause
- osteoporosis
- obesity
- bone

Journal of Molecular Endocrinology (2019) **63**, R73–R80

First-in-class humanized FSH blocking antibody targets bone and fat

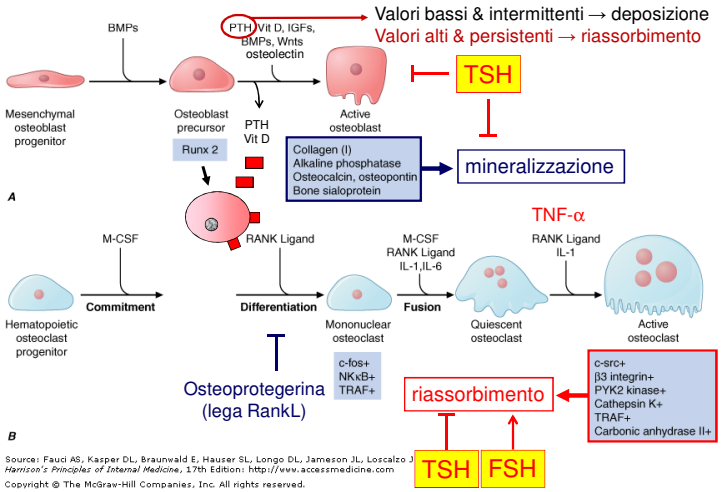
Sakshi Gera[a], Damini Sant[a], Shozeb Haider[b], Funda Korkmaz[a], Tan-Chun Kuo[a], Mehr Mathew[a], Helena Perez-Pena[b], Honglin Xie[c], Hao Chen[d], Rogerio Batista[a], Kejun Ma[a,e], Zhen Cheng[d], Elina Hadelia[a], Cemre Robinson[a], Anne Macdonald[a], Sari Miyashita[a], Anthony Williams[a], Gregory Jebian[a], Hirotaka Miyashita[a], Anisa Gumerova[a], Kseniia Ievleva[a], Pinar Smith[a], Jiahuan He[f], Vitaly Ryu[a], Victoria DeMambro[g], Matthew A. Quinn[h], Marcia Meseck[i], Se-Min Kim[a], T. Rajendra Kumar[f], Jameel Iqbal[a], Maria I. New[a,1], Daria Lizneva[a], Clifford J. Rosen[g], Aaron J. Hsueh[f], Tony Yuen[a], and Mone Zaidi[a,1]

Significance

We report the development and characterization of a first-in-class humanized antibody to follicle-stimulating hormone (FSH). We have shown previously that blocking FSH action on its receptor increases bone mass, reduces body fat, and enhances energy expenditure. Furthermore, FSH has been reported to increase serum cholesterol. Therefore, an anti-FSH agent has the potential of preventing and treating obesity, osteoporosis, and hypercholesterolemia, diseases that affect millions of women and men worldwide. Our study provides the framework for further preclinical and subsequent clinical testing of our humanized antibody to FSH.

PNAS | **November 17, 2020** | vol. 117 | no. 46 | **28971–28979**

Osteoblasti & osteoclasti - regolazione



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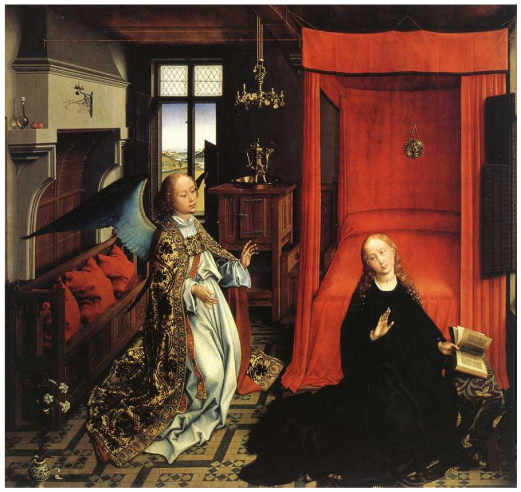

Rogier van der Weyden, Annunciazione (c. 1440) Museo del Louvre, Parigi

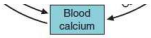

FIGURE 423-5 Schematic representation of the hormonal control loop for vitamin D metabolism and function. A reduction in the serum calcium below ~2.2 mmol/L (8.8 mg/dL) prompts a proportional increase in the secretion of parathyroid hormone (PTH) and so mobilizes additional calcium from the bone. PTH promotes the synthesis of $1,25(OH)_2D$ in the kidney, which in turn stimulates the mobilization of calcium from bone and intestine and regulates the synthesis of PTH by negative feedback.

The second hydroxylation, required for the formation of the mature hormone, occurs in the kidney (Fig. 423-5). The 25-hydroxyvitamin D-1α-hydroxylase is a tightly regulated cytochrome P450–like mixed-function oxidase expressed in the proximal convoluted tubule cells of the kidney. PTH and hypophosphatemia are the major inducers of this microsomal enzyme, whereas calcium, FGF23, and the enzyme's product, $1,25(OH)_2D$, repress it. The 25-hydroxyvitamin D-1α-hydroxylase is also present in epidermal keratinocytes, but keratinocyte production of $1,25(OH)_2D$ is not thought to contribute to circulating levels of this hormone. In addition to being present in the trophoblastic layer of the placenta, the 1α-hydroxylase is produced by macrophages associated with granulomas and lymphomas. In these latter pathologic states, the activity of the enzyme is induced by interferon γ and TNF-α but is not regulated by calcium or $1,25(OH)_2D$; therefore, hypercalcemia, associated with elevated levels of $1,25(OH)_2D$, may be observed. Treatment of sarcoidosis-associated hypercalcemia with glucocorticoids, ketoconazole, or chloroquine reduces $1,25(OH)_2D$ production

The VDR is expressed in a wide range of cells and tissues. The molecular actions of $1,25(OH)_2D$ have been studied most extensively in tissues involved in the regulation of mineral ion homeostasis. This hormone is a major inducer of calbindin 9K, a calcium-binding protein expressed in the intestine, which is thought to play an important role in the active transport of calcium across the enterocyte. The two major calcium transporters expressed by intestinal epithelia, TRPV5 and TRPV6 (transient receptor potential vanilloid), are also vitamin D responsive. By inducing the expression of these and other genes in the small intestine, $1,25(OH)_2D$ increases the efficiency of intestinal calcium absorption, and it also has been shown to have several important actions in the skeleton. The VDR is expressed in osteoblasts and regulates the expression of several genes in this cell. These genes include the bone matrix proteins osteocalcin and osteopontin, which are upregulated by $1,25(OH)_2D$, in addition to type I collagen, which is transcriptionally repressed by $1,25(OH)_2D$. Both $1,25(OH)_2D$ and PTH induce the expression of RANK ligand, which promotes osteoclast differentiation and increases osteoclast activity, by binding to RANK on osteoclast progenitors and mature osteoclasts. This is the mechanism by which $1,25(OH)_2D$ induces bone resorption. However, the skeletal features associated with VDR-knockout mice (rickets, osteomalacia) are largely corrected by increasing calcium and phosphorus intake, underscoring the importance of vitamin D action in the gut.

The VDR is expressed in the parathyroid gland, and $1,25(OH)_2D$ has been shown to have antiproliferative effects on parathyroid cells and to suppress the transcription of the PTH gene. These effects of $1,25(OH)_2D$ on the parathyroid gland are an important part of the rationale for current therapies directed at preventing and treating hyperparathyroidism associated with renal insufficiency.

The VDR is also expressed in tissues and organs that do not play a

NEWS AND VIEWS
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A new *Twist* in kidney fibrosis

Yossi Ovadya & Valery Krizhanovsky

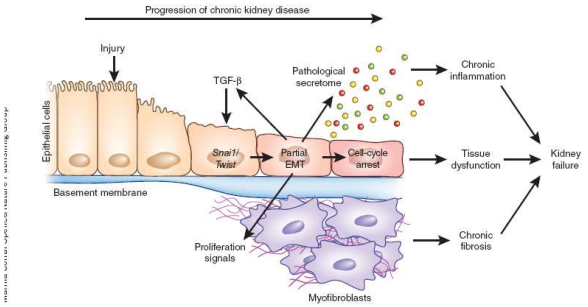

Figure 1 Partial EMT promotes chronic kidney disease. Grande *et al.*[6] and Lovisa *et al.*[7] provide new insights into mechanisms of EMT contribution to kidney fibrosis. After injury of the epithelia, TGF-β promotes *Snail1* and *Twist* expression, which activate the EMT program in the epithelial cells. The authors find that these epithelial cells undergo an incomplete EMT; they remain attached to the basement membrane and promote kidney disease by several mechanisms. In a cell-autonomous manner, a partial EMT leads to cell-cycle arrest, halting further proliferation and repair, which leads to tissue dysfunction. The partial EMT also drives proliferation of myofibroblasts by the secretion of growth factors, including TGF-β. Moreover, this program fuels chronic inflammation. In the long term, these three disease-promoting axes converge into systemic failure of kidney function.

The Journal of Clinical Investigation COMMENTARY

A generic crystallopathic model for chronic kidney disease progression

Orson W. Moe

J Clin Invest. 2021;131(16):e151858 https://doi.org/10.1172/JCI151858

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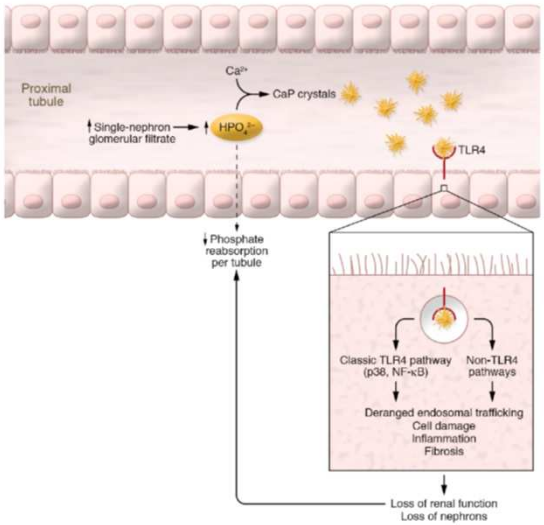
Chronic kidney disease (CKD) has reached epidemic proportions globally. The natural course of chronic kidney disease is almost uniformly progressive, albeit at different rates in different individuals. The downhill course appears to pervade kidney diseases of all etiologies and seems to spiral down a self-perpetuating vortex, even if the original insult is ameliorated or controlled. In this issue of the *JCI*, Shiizaki, Tsubouchi, and colleagues proposed a model of renal tubule luminal calcium phosphate crystallopathy that accounts for renal function demise. Calcium phosphate crystals attached to TLR4 and underwent endocytosis at the brush border, triggering inflammation and fibrosis. This mechanism might operate in different kinds of kidney disease, with a theoretical phosphate concentration threshold in the proximal tubular lumen, beyond which is triggered undesirable downstream effects that eventuate in loss of renal function. If this model parallels human CKD, clinicians may focus efforts on determining phosphate exposure in the proximal tubular lumen.



The Journal of Clinical Investigation RESEARCH ARTICLE

Calcium phosphate microcrystals in the renal tubular fluid accelerate chronic kidney disease progression

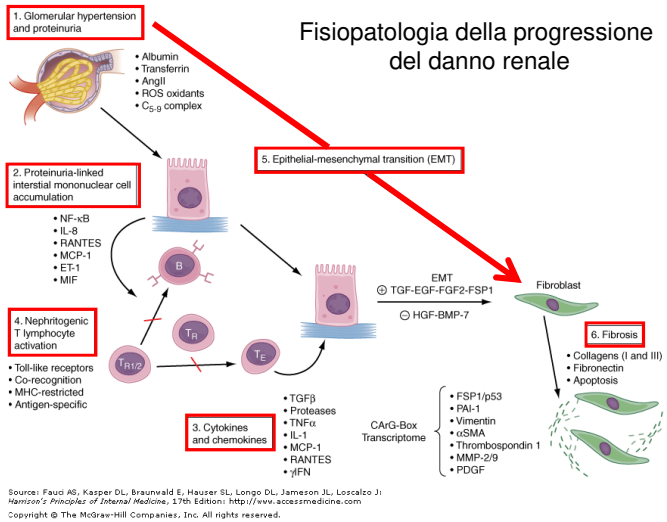
Kazuhiro Shiizaki,[1,2] Asako Tsubouchi,[3] Yutaka Miura,[1] Kinya Seo,[4] Takahiro Kuchimaru,[5] Hirosaka Hayashi,[1] Yoshitaka Iwazu,[1,6,7] Marina Miura,[1,6] Batpurev Battulga,[8] Nobuhiko Ohno,[8,9] Toru Hara,[10] Rina Kunishige,[3] Mamiko Masutani,[11] Keita Negishi,[12] Kazuomi Kario,[12] Kazuhiko Kotani,[7] Toshiyuki Yamada,[7] Daisuke Nagata,[6] Issei Komuro,[13] Hiroshi Itoh,[14] Hiroshi Kurosu,[1] Masayuki Murata,[3] and Makoto Kuro-o[1]

The Western pattern diet is rich not only in fat and calories but also in phosphate. The negative effects of excessive fat and calorie intake on health are widely known, but the potential harms of excessive phosphate intake are poorly recognized. Here, we show the mechanism by which dietary phosphate damages the kidney. When phosphate intake was excessive relative to the number of functioning nephrons, circulating levels of FGF23, a hormone that increases the excretion of phosphate per nephron, were increased to maintain phosphate homeostasis. FGF23 suppressed phosphate reabsorption in renal tubules and thus raised the phosphate concentration in the tubule fluid. Once it exceeded a threshold, microscopic particles containing calcium phosphate crystals appeared in the tubule lumen, which damaged tubule cells through binding to the TLR4 expressed on them. Persistent tubule damage induced interstitial fibrosis, reduced the number of nephrons, and further boosted FGF23 to trigger a deterioration spiral leading to progressive nephron loss. In humans, the progression of chronic kidney disease (CKD) ensued when serum FGF23 levels exceeded 53 pg/mL. The present study identified calcium phosphate particles in the renal tubular fluid as an effective therapeutic target to decelerate nephron loss during the course of aging and CKD progression.

Reference information: *J Clin Invest*. 2021;131(16):e145693. https://doi.org/10.1172/JCI145693.

Figure 1. Model of renal tubular crystallopathy and CKD progression proposed by Shiizaki, Tsubouchi, and coworkers. In CKD of any etiology, high filtration in intact nephrons and reduced phosphate reabsorption driven by high parathyroid hormone and FGF23, and CKD itself, increase luminal phosphate concentrations. When calcium phosphate reaches a certain threshold in the end of the proximal tubule, crystals form and bind to brush border TLR4, which secures the crystals on the cell surface, internalizes the crystals, and activates a series of cascades. Subsequent damage of the tubules sets off inflammation and fibrosis in the tubulointerstitium, engendering further loss of renal function. The process reiterates in a vicious cycle.

Fisiopatologia della progressione del danno renale



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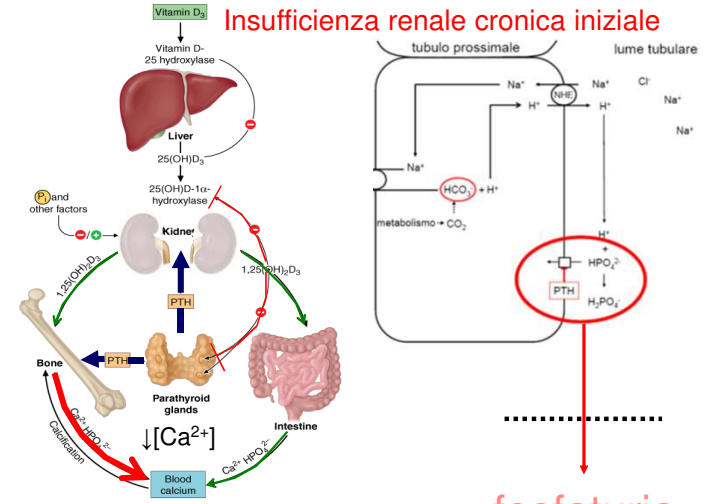
Insufficienza renale cronica iniziale



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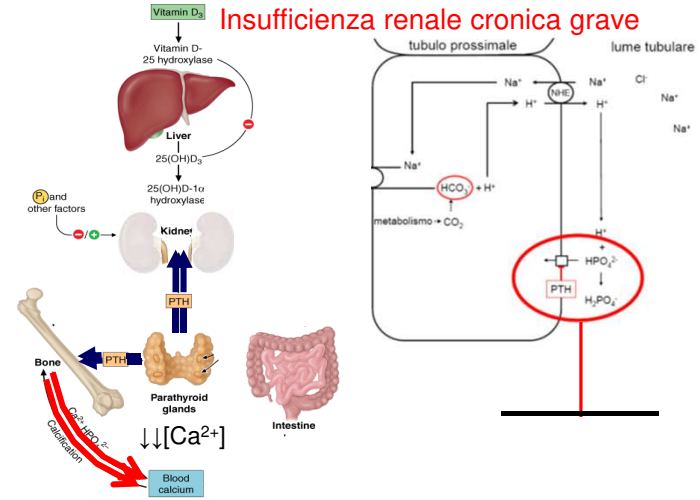
fosfaturia

Insufficienza renale cronica grave



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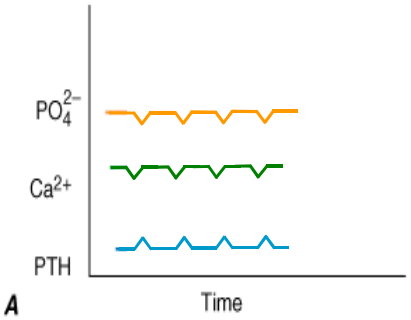
NORMALE



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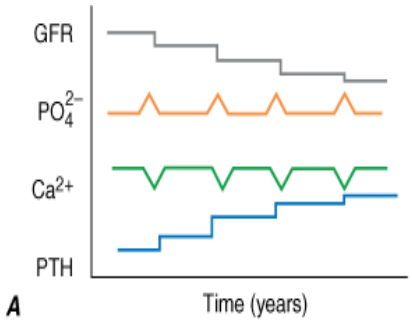
modificata

INSUFFICIENZA RENALE CRONICA



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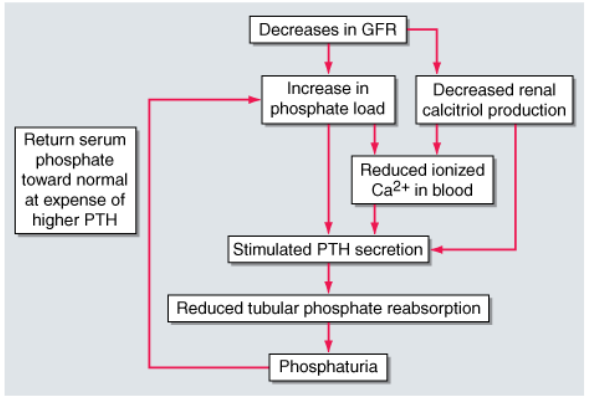

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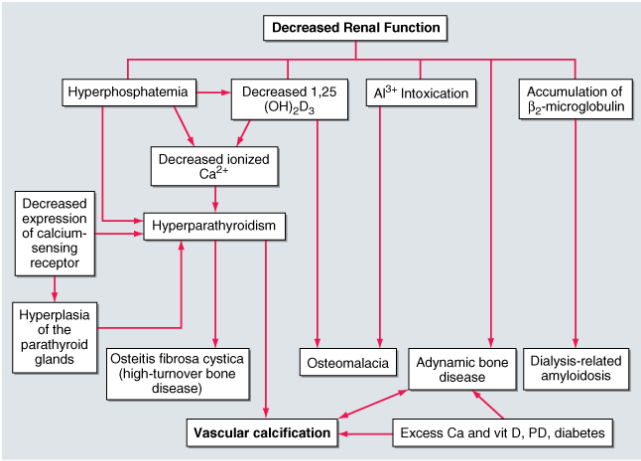

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Review > J Nephrol. Mar-Apr 2005;18(2):117-22.

Adynamic bone disease: an update and overview

Giorgio Coen [1]

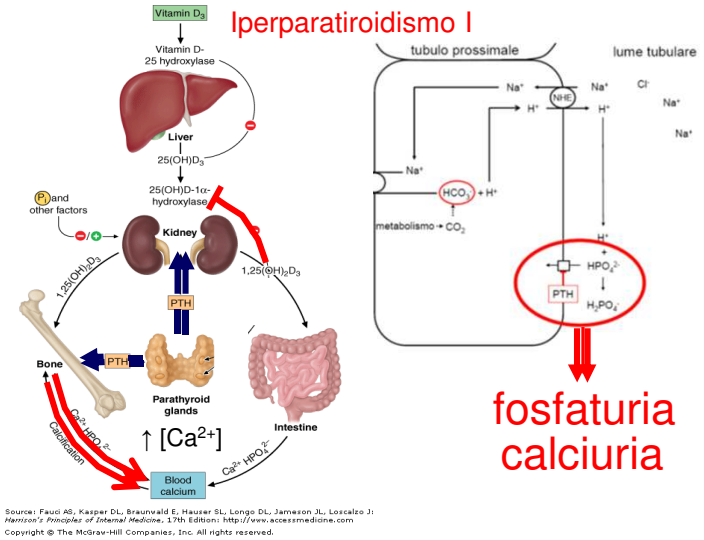
Affiliations + expand

PMID: 15931639

Abstract

Adynamic bone disease (ABD) is a variety of renal osteodystrophy characterized by reduced osteblasts and osteoclasts, no accumulation of osteoid and markedly low bone turnover. It has been found in a relatively high percentage of patients on dialysis, either peritoneal or hemodialysis, but also in CKD patients on conservative treatment. The histologic pattern of ABD is generally associated to low levels of PTH. However, PTH serum levels in CKD are generally higher than normal even when associated to ABD. Therefore, it is felt that, basically in uremia, bone tissue is resistant to PTH, so that a relative reduction of its levels is able to induce the emergence of a low turnover state. Several factors theoretically responsible for skeletal resistance to PTH, and able to slow bone turnover have been considered. Among these are downregulation of PTH receptors in bone cells, increased levels of osteoprotegerin, decreased production and circulating levels of bone morphogenetic proteins, the peripheral effect of leptin and also a possible effect of increased N-terminal truncated PTH molecular species, which have been found to counteract the whole molecule, PTH 1-84 on the bone. In conclusion, ABD should probably be considered a skeletal condition induced by overtreatment of secondary hyperparathyroidism and not a disease. However, its development reveals a deranged ability of uremic bone to maintain a normal bone turnover, when PTH serum levels decrease beyond relatively low levels, which would be considered normal in the general population.

Iperparatiroidismo I



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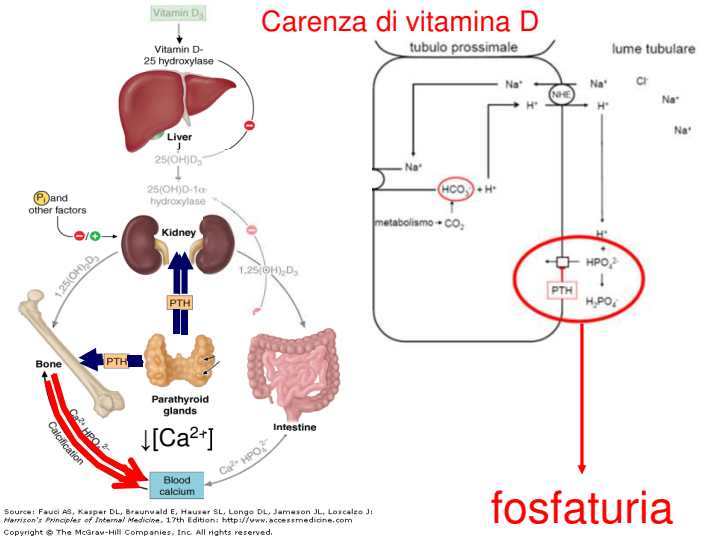
Carenza di vitamina D



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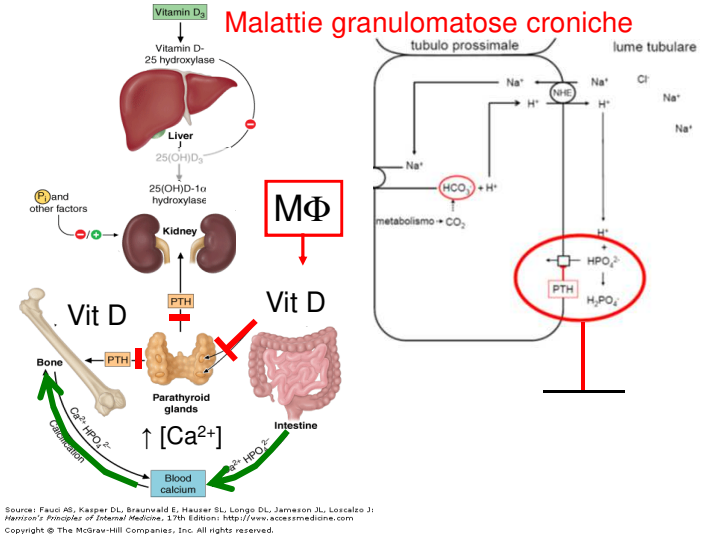
Malattie granulomatose croniche



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Cause di ipercalcemia

Paratiroidee
- Iperparatiroidismo I (adenoma, neoplasie multiendocrine)
- Terapia con Li^+
- Familiare (ipocalciurica)

Vitamina D
- Intossicazione D3
- Malattie granulomatose croniche

Alto turnover osso
- Ipertiroidismo (e basso TSH)
- Elevato FSH (osteoporosi postmenopausa)
- Immobilizzazione
- Tiazidi
- Intossicazione da vitamina A

Insufficienza renale: conflitto fra stimoli
- ipercalcemizzanti (iperplasia delle paratiroidi)
- ipocalcemizzanti (ritenzione Pi, diminuito assorbim. intest.)

Cause di ipocalcemia

Carenza PTH

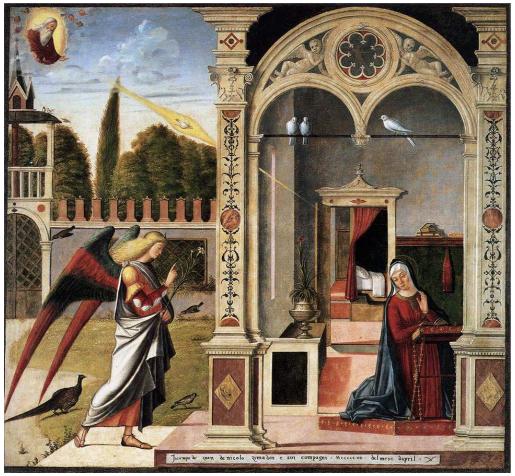
- Ereditaria
- Acquisita (rimozione chirurgica)
- Ipomagnesiemia

Vitamina D

- Insufficienza renale cronica
- carenza alimentare (e/o deficit di esposizione solare)
- malassorbimento
- malattie ereditarie del recettore

Alterazione legame del calcio circolante

- iperfosfatemia
- insufficienza renale acuta



Vittore Carpaccio, Annunciazione (1504) Galleria Franchetti, Ca' d'Oro