7-10 novembre 2013, Bari

12° Congresso Nazionale AME
6th Joint Meeting with AACE

Update in Endocrinologia Clinica

	L'Osteomalacia
Coordinatore:	M. Zini (RE)
Moderatori:	A. Santonati (RM), A. Scillitani (SGR)
	1. Malattie del metabolismo osseo: non solo osteoporosi (F. Vescini, UD)
	2. Eziopatogenesi dell'osteomalacia (A. Scillitani, SGR)
	3. Inquadramento diagnostico (R. Cesareo, LT)
	4. Gestione terapeutica (C. Eller-Vainicher, MI)
	5. Dalla teoria alla pratica: discussione interattiva (D. Rendina, NA)
	6. Take home messages (M. Zini, RE)

OSTEOMALACIA

L'Osteomalacia è caratterizzata da un'insufficiente mineralizzazione del tessuto osteoide neoformato presso i siti di rimodellamento osseo o di apposizione periostale ed endostale.

Malattie associate a bassa massa ossea e/o fratture da fragilità

- **Osteoporosi**
  - primitiva
  - secondaria
- **Osteomalacia**
  - **resistenza/carenza di vitamina D**
  - **ipofosfatemia**
  - **ipofosfatasia**
- **Altre anomalie del tessuto osseo/connettivo**
  - Osteogenesi imperfetta
  - Displasia fibrosa
  - Omocistinuria
  - Sindrome di Marfan
  - Malattia di Gaucher

PREVALENZA DI OSTEOMALACIA IN PAZIENTI CON FRATTURA DI ANCA

Autore	numero di pazienti	osteomalacia (%)
Chalmers et al., 1969	130	20
Hodgkinson, 1971	35	0
Aaron et al., 1974	125	37
Faccini et al., 1976	51	"many"
Wootton et al., 1979	80	8
Hoikka et al., 1982	50	24
Lips et al., 1982	89	11
Johnston et al., 1985	32	10
Wilton et al., 1987	201	2

media 14 %

Lips P, 1992

From the *Primer on the Metabolic Bone Diseases and Disorders of Mineral Metabolism, 7th Edition*.
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Figure 1

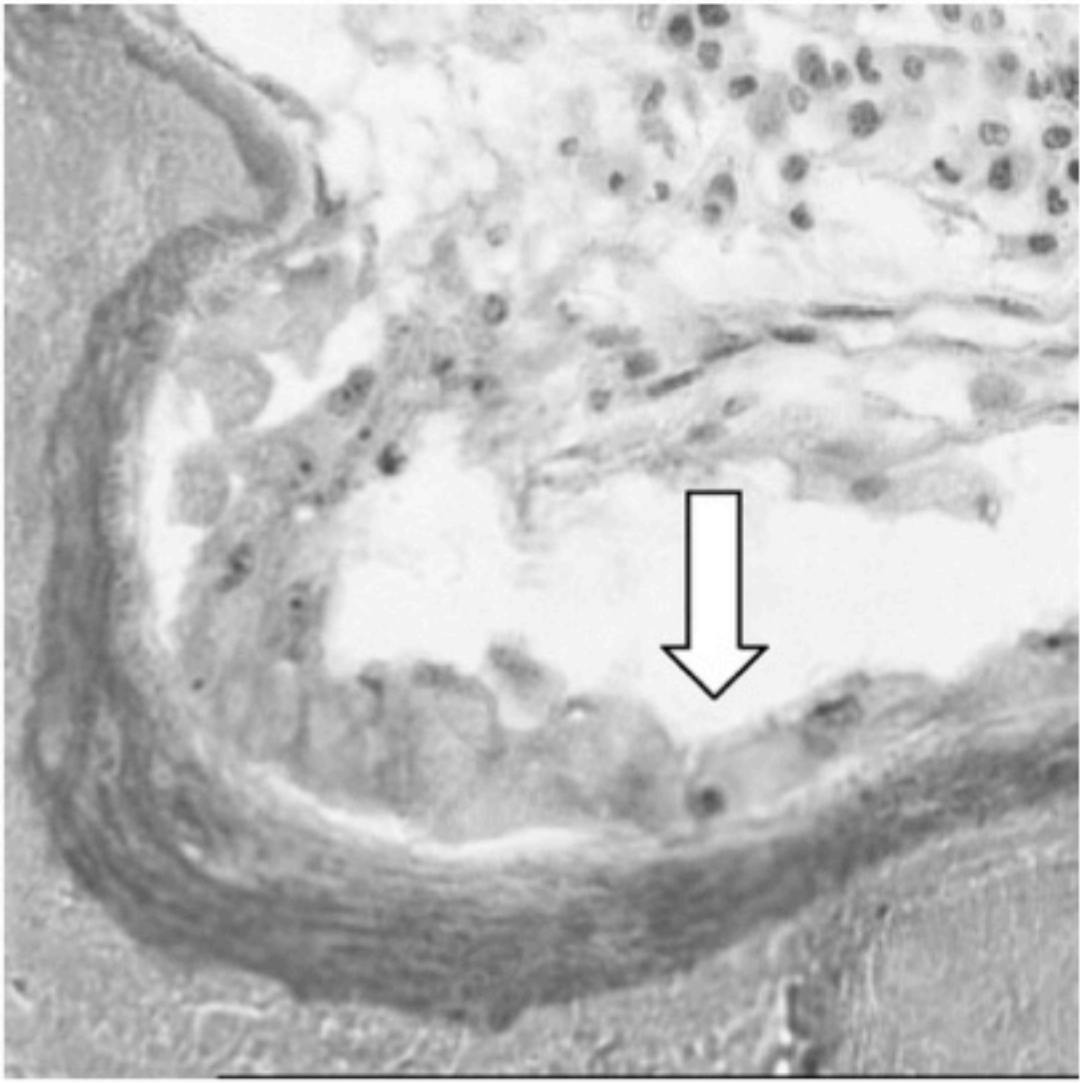

Figure 1 A normal bone-forming surface. Unmineralized osteoid is covered with plump osteoblasts, as identified by the arrow.

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Figure 2

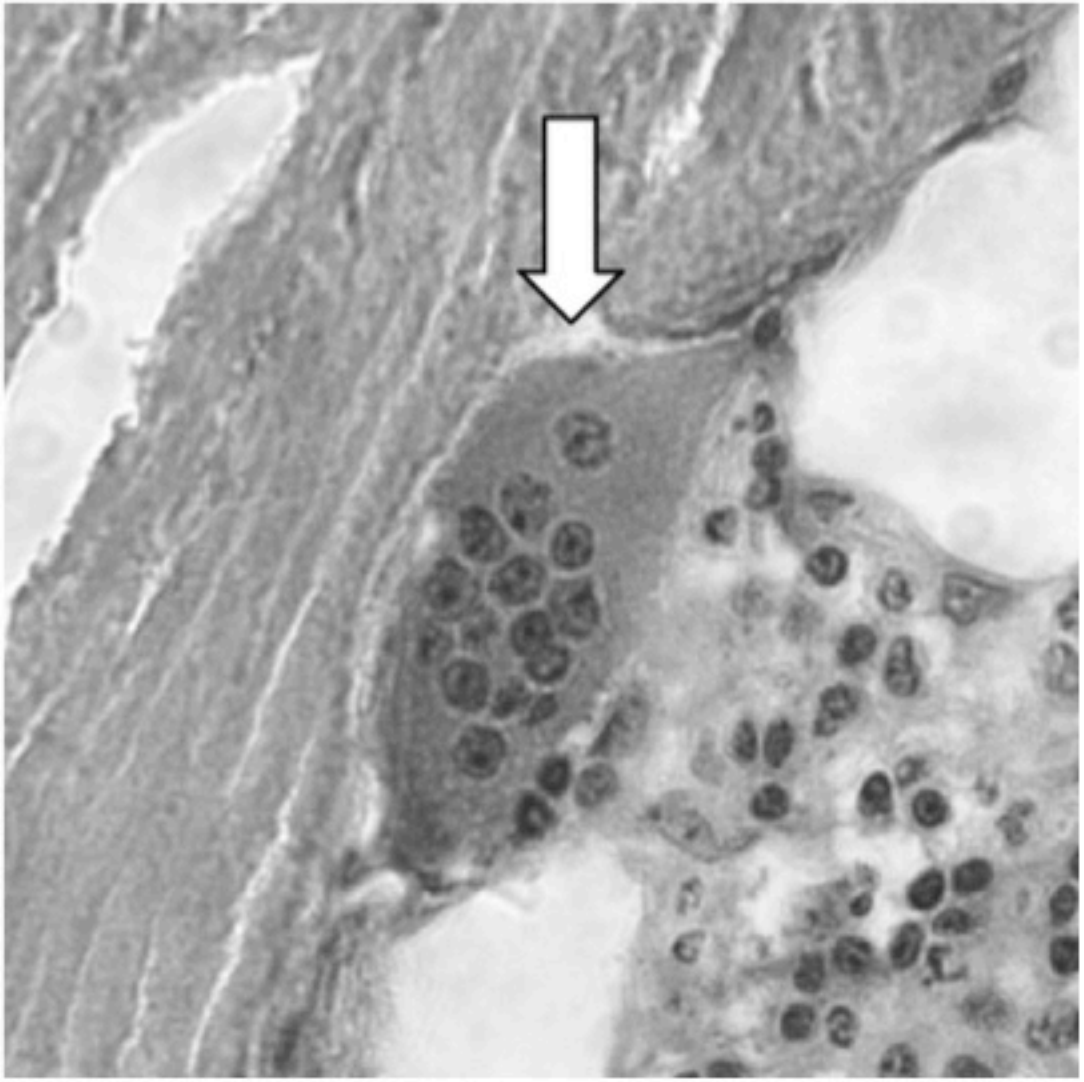

Figure 2 A normal bone-resorbing surface. The arrow locates a multinucleated osteoclast in a Howship's lacuna.

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Figure 2

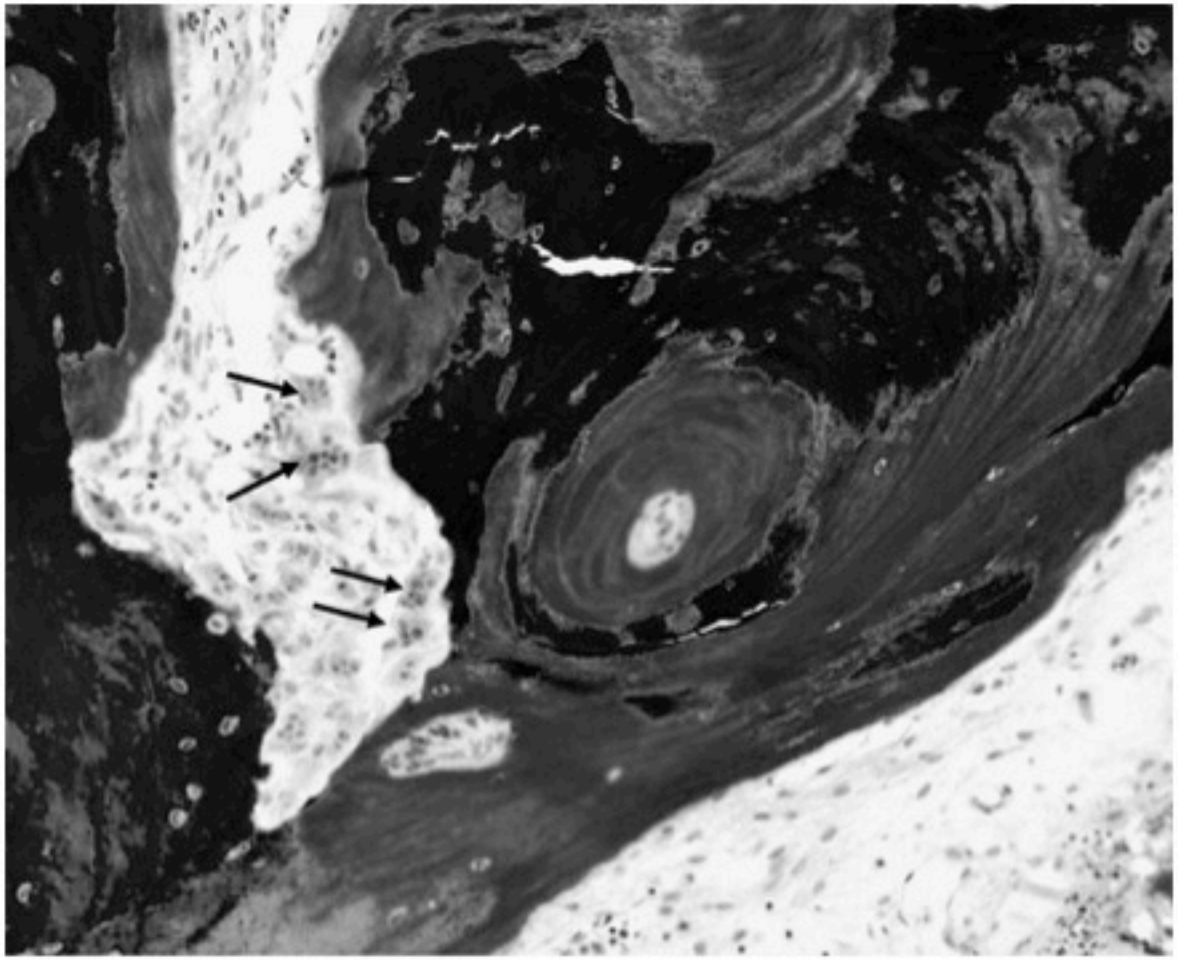
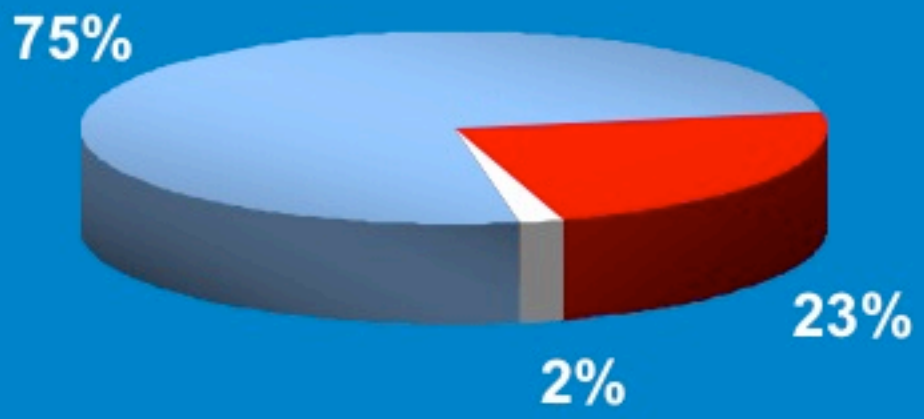


Figure 2 Osteomalacia in a patient with celiac disease. Goldner stain: mineralized bone is black and osteoid tissue is gray. Besides thick osteoid seams, increased bone resorption by multinucleated osteoclasts (arrows) is visible.

Esame istomorfometrico di 119 biopsie della cresta iliaca di pazienti con diagnosi clinica di osteoporosi



- 89 pazienti (~75 %) con osteoporosi
- 28 pazienti (~23 %) con discreto deficit di mineralizzazione
- 2 pazienti (~2 %) con franca osteomalacia

Ballanti P & Bonucci E, GIMME 1988

From the *Primer on the Metabolic Bone Diseases and Disorders of Mineral Metabolism, 7th Edition*.
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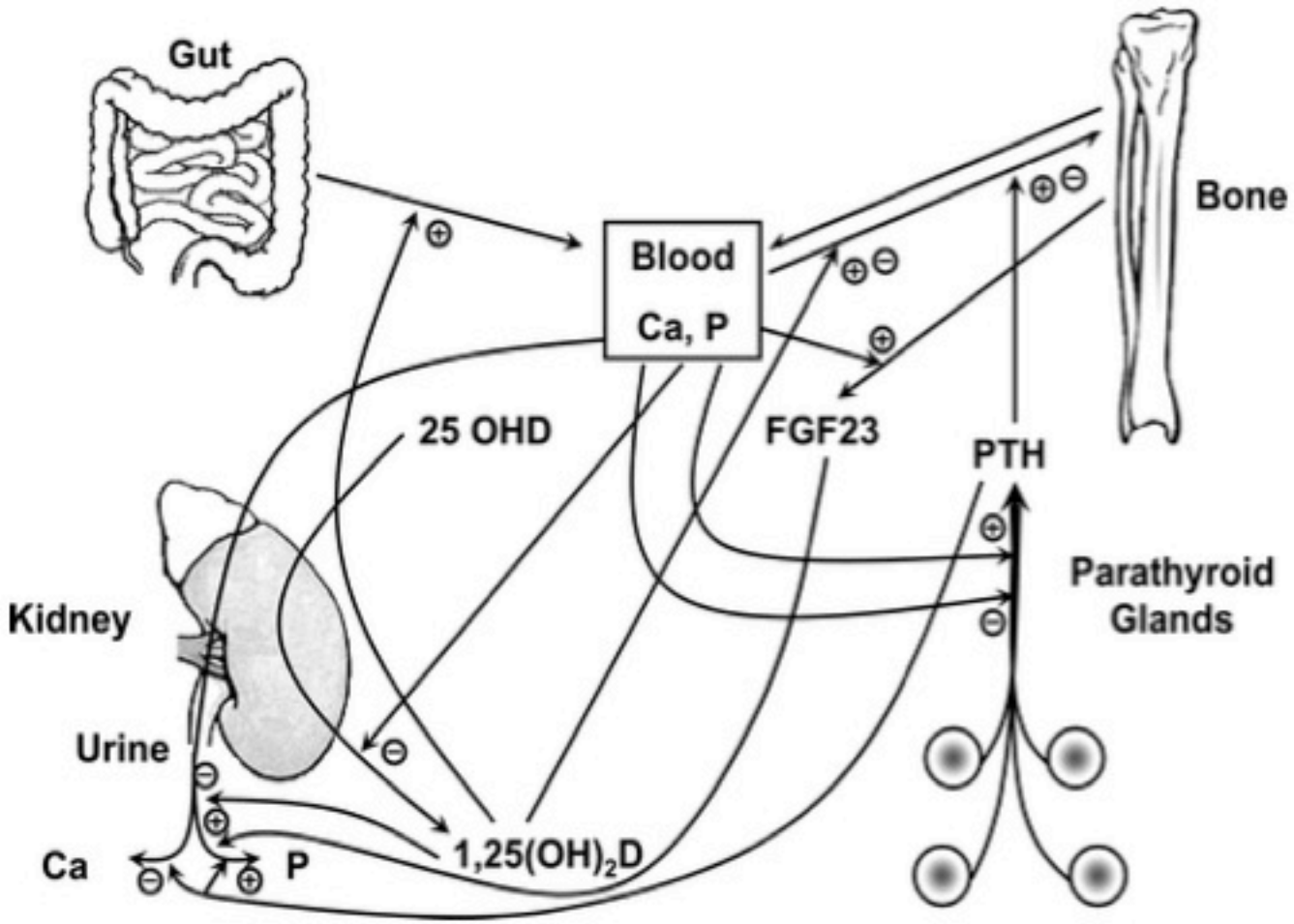

Figure 3 1,25(OH)2D3 interacts with other hormones, in particular FGF23 and PTH, to regulate calcium and phosphate homeostasis. As noted in the legend to figure 2, FGF23 inhibits whereas PTH stimulates 1,25(OH)2D3 production by the kidney. In turn 1,25(OH)2D3 inhibits PTH production but stimulates that of FGF23. Calcium and phosphate in turn regulate FGF23, PTH, and so 1,25(OH)2D3 indirectly.

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Table 2. Causes of Rickets and Osteomalacia

- Vitamin D–related rickets/osteomalacia
  - Nutritional: low sunshine exposure, low dietary intake
  - Malabsorption: celiac disease, Crohn's disease, gastrectomy, gastric bypass, bowel resection, pancreatitis
  - Impaired hydroxylation in liver: severe chronic liver disease
  - Impaired renal function: renal osteodystrophy/osteomalacia
  - Increased renal loss: nephrotic syndrome
  - Increased catabolism: anti-convulsant therapy
  - Inborn errors of metabolism
  - Nonfunctioning 25-hydroxylase (OMIM 600081)
  - Absent 1α-hydroxylase: pseudovitamin D deficiency rickets (vitamin D–dependent rickets type 1 OMIM 264700)
  - Nonfunctioning VDR: hereditary vitamin D resistant rickets (vitamin D–dependent rickets type 2, OMIM 277440)
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  - X-linked hypophosphatemic rickets, OMIM 307800*
  - Autosomal dominant hypophosphatemic rickets, OMIM 193100*
  - Hereditary hypophosphatemic rickets with hypercalciuria, OMIM 241530
  - Oncogenic osteomalacia*
  - Fanconi syndrome, metabolic acidosis
- Calcium deficiency: very low calcium intake in children
- Miscellaneous:
  - Aluminium intoxication
  - Cadmium intoxication
  - Etidronate overdose (in Paget's disease)
  - Hypophosphatasia, OMIM 146300

* Associated with low serum $1,25(OH)_2D$.

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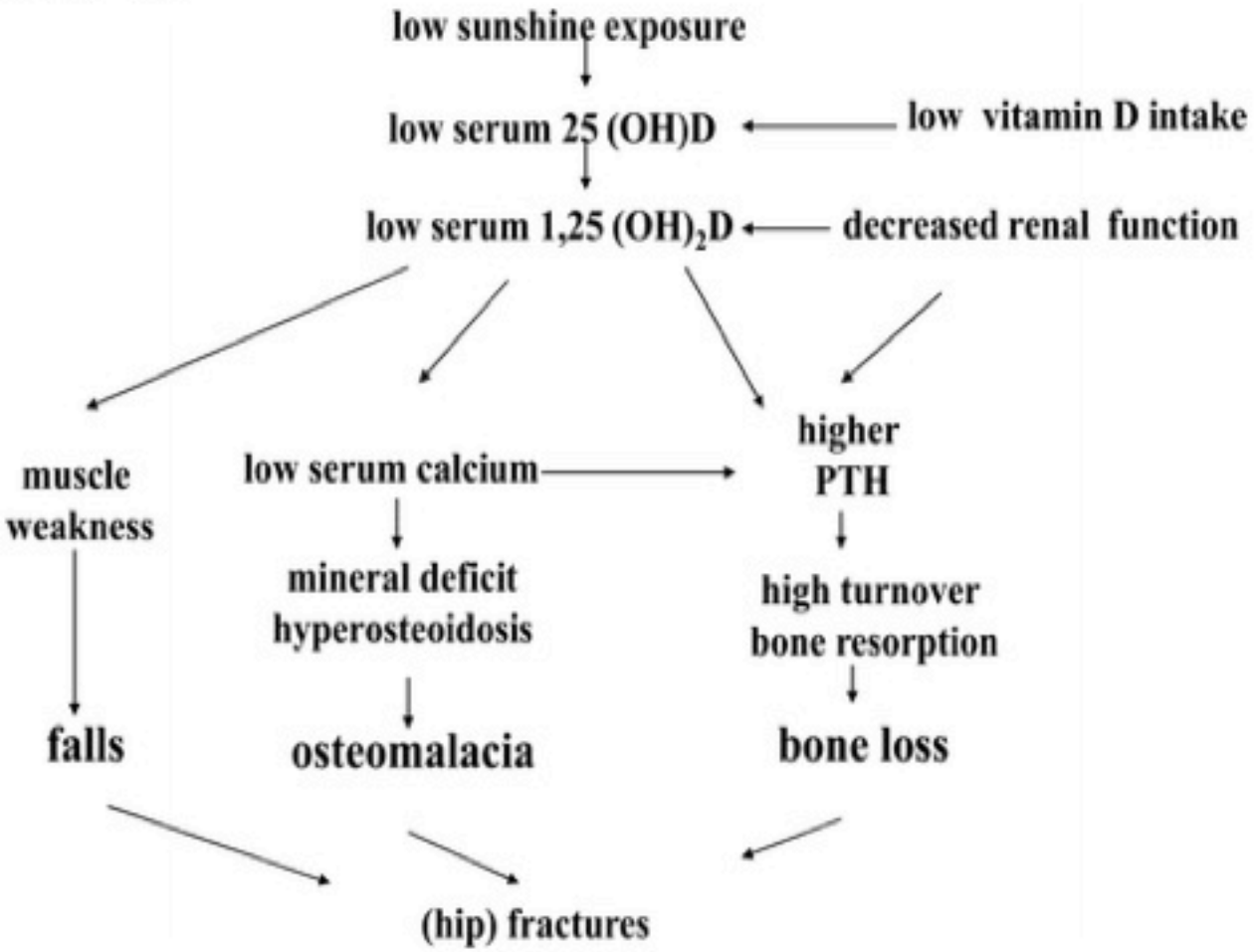
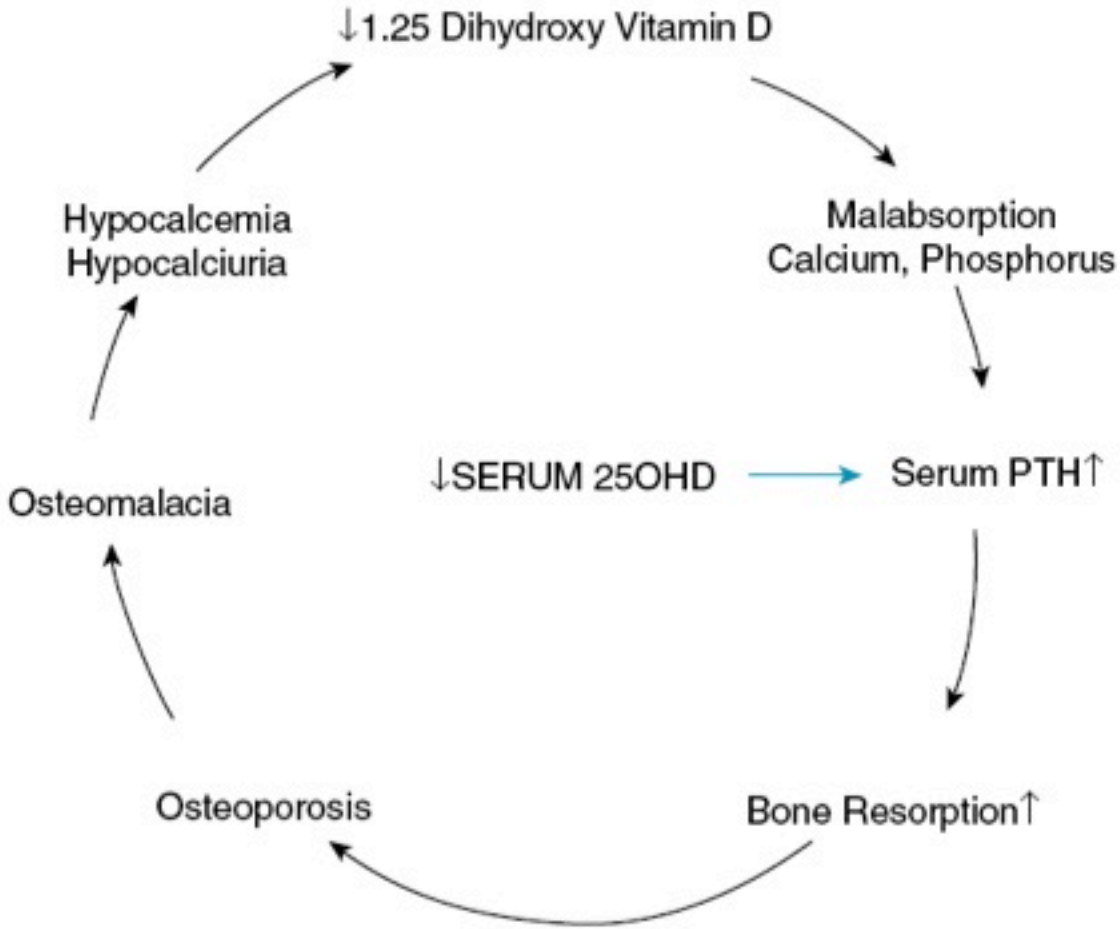


Figure 1 The pathway from vitamin D deficiency to falls and fractures.



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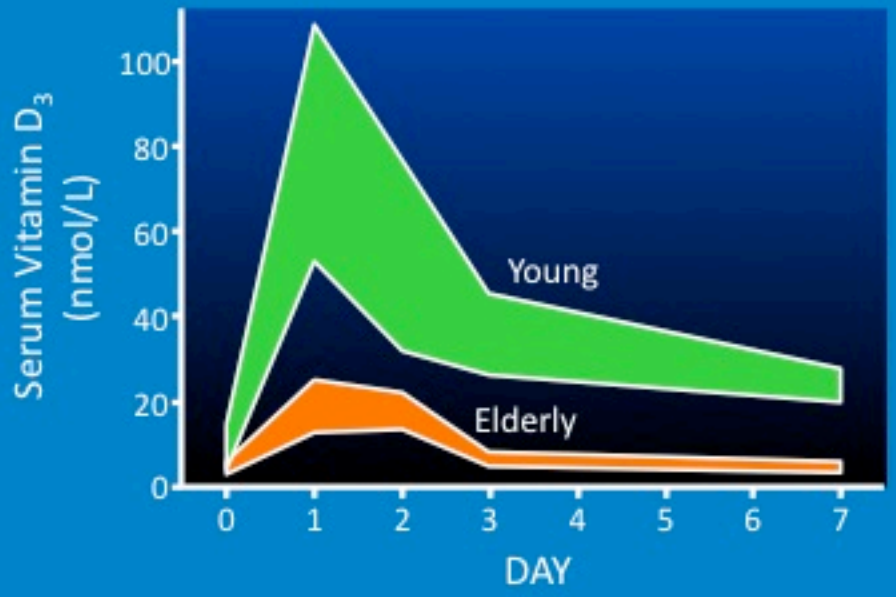
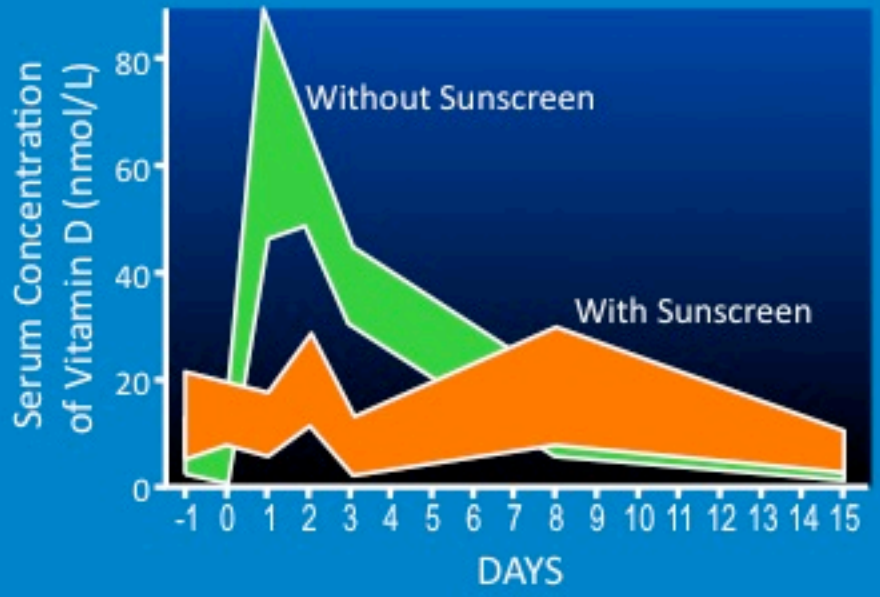
Factors that alter the cutaneous production of vitamin D3

- Age
- Melanin content of the skin
- Use of sunscreens (sun protection factor 8 reduces production of vitamin D by 95%)
- Time of day (early morning and late afternoon)
- Latitude (above 37° latitude, during winter, marked decreases in the number of UVB photons reaching the earth's surface)
- Season

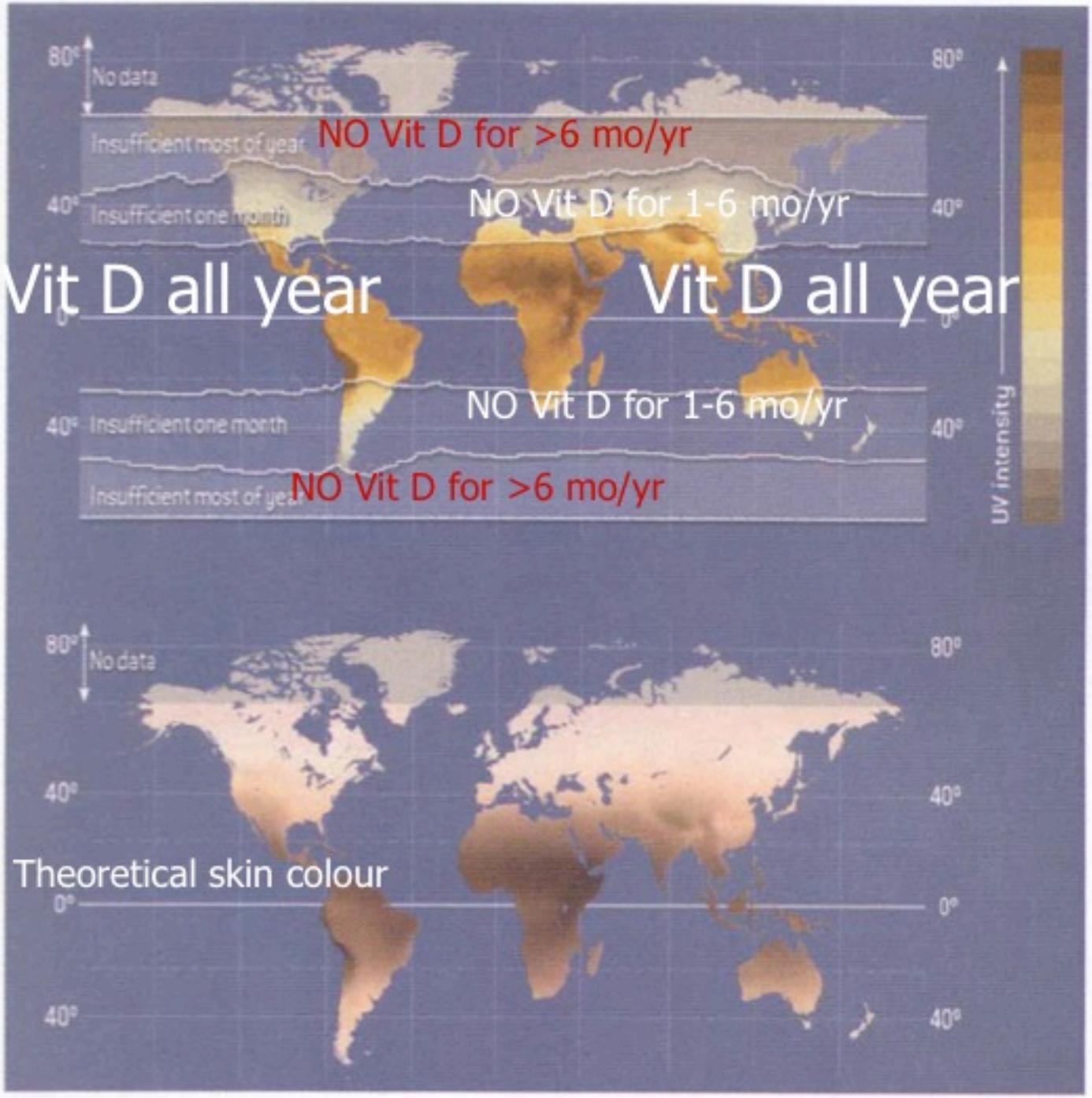
Circulating concentrations of vitamin D_3 in response to a whole-body exposure



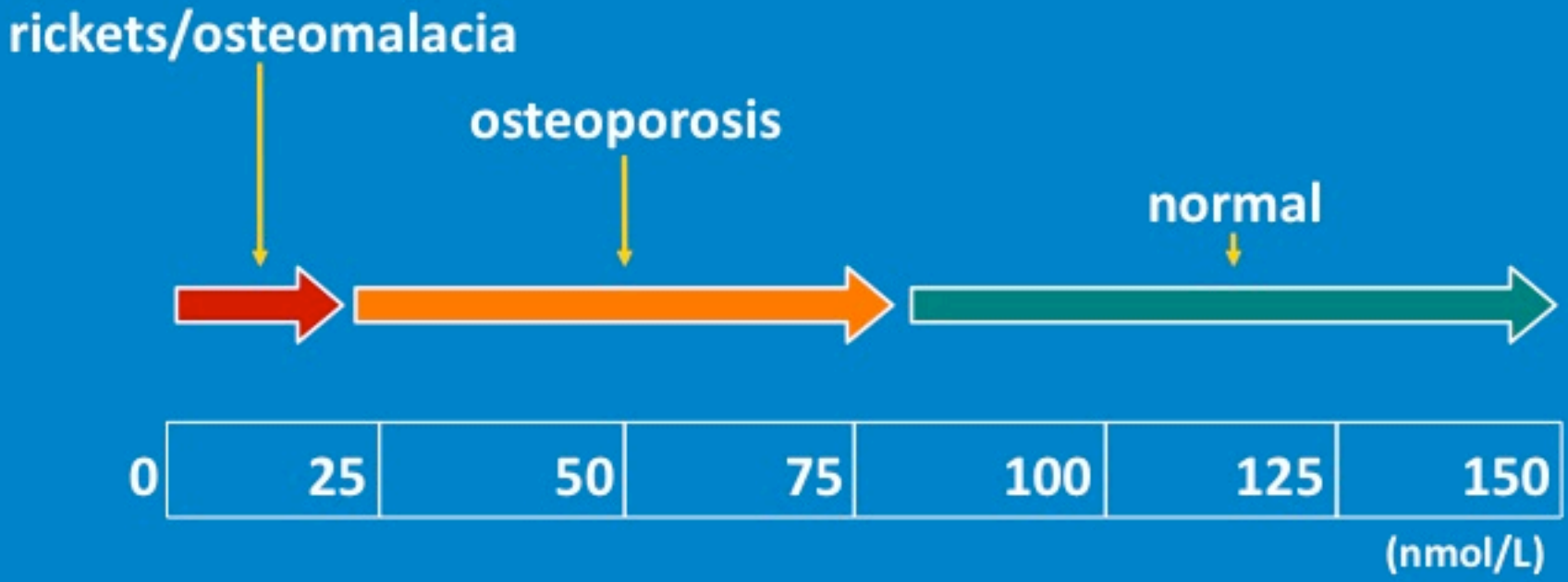


Holick M.F. et al., Am. J. Clin. Nutr., 1994

Number of Months that UVB from sunshine cannot produce vitamin D3 in skin

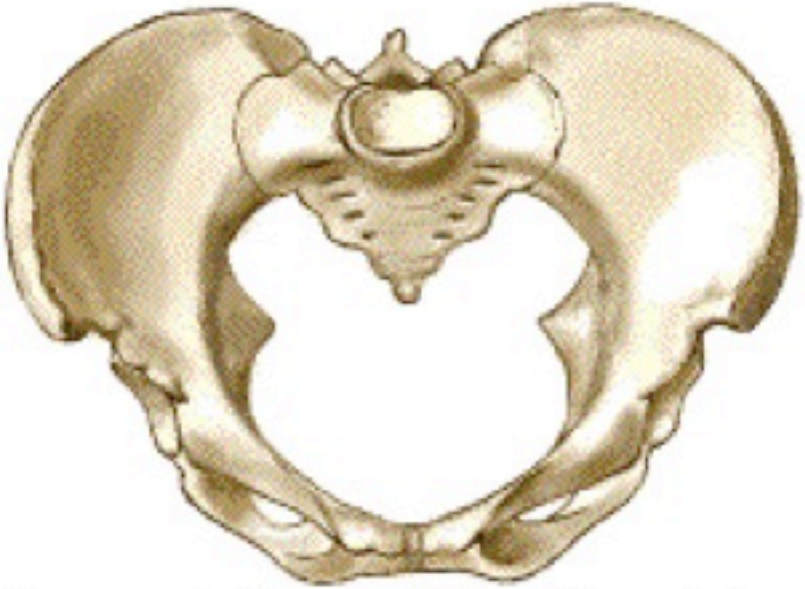


Suggested mapping of the principal vitamin D – related bone diseases onto the serum 25(OH)D concentration continuum

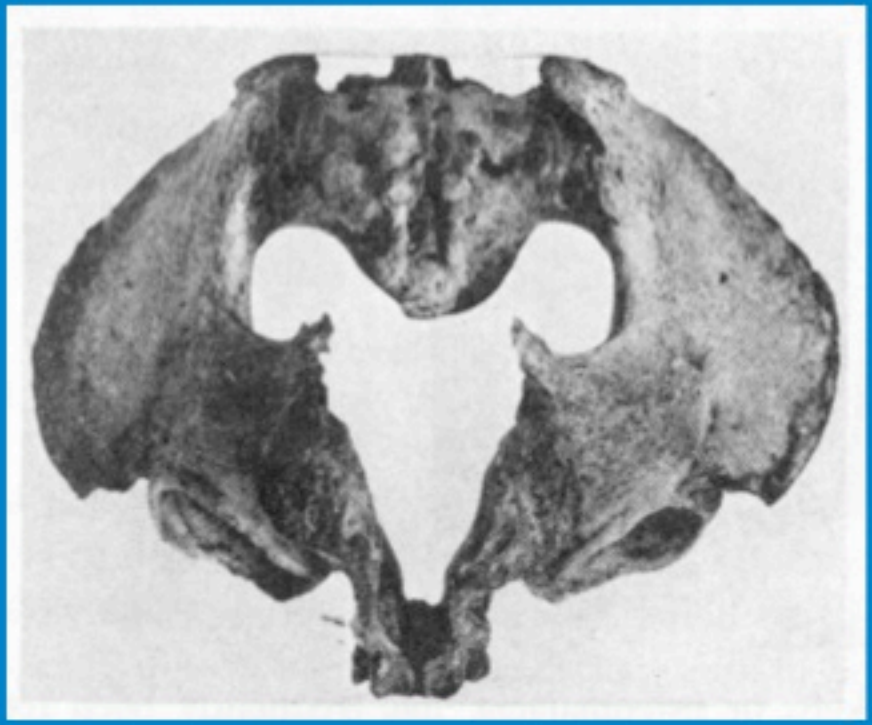


Heaney R.P., Am J Clin Nutr, 2004

Childhood lack of vitamin D causes rickets



Normal shape of female pelvis



Contracted pelvis, in a case of osteomalacia (adult rickets).

Normal childbirth would be impossible.

Vieth 2001. Nutritional Aspects of Osteoporosis, Chapter 17, ed P Burckhardt, RP Heaney, B Dawson-Hughes; Academic Press

From the *Primer on the Metabolic Bone Diseases and Disorders of Mineral Metabolism, 7th Edition*.
www.asbmrprimer.org

Figure 4

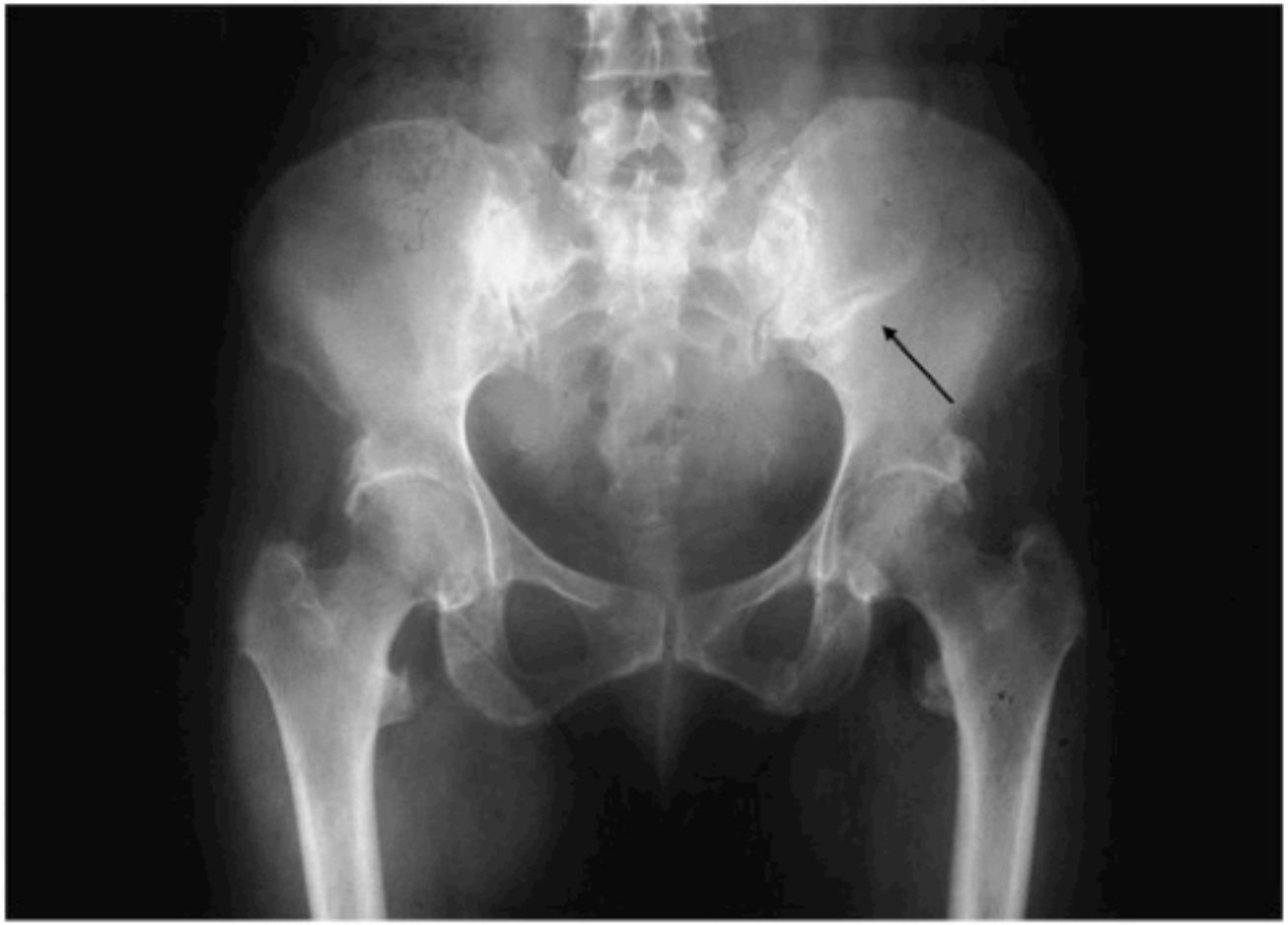
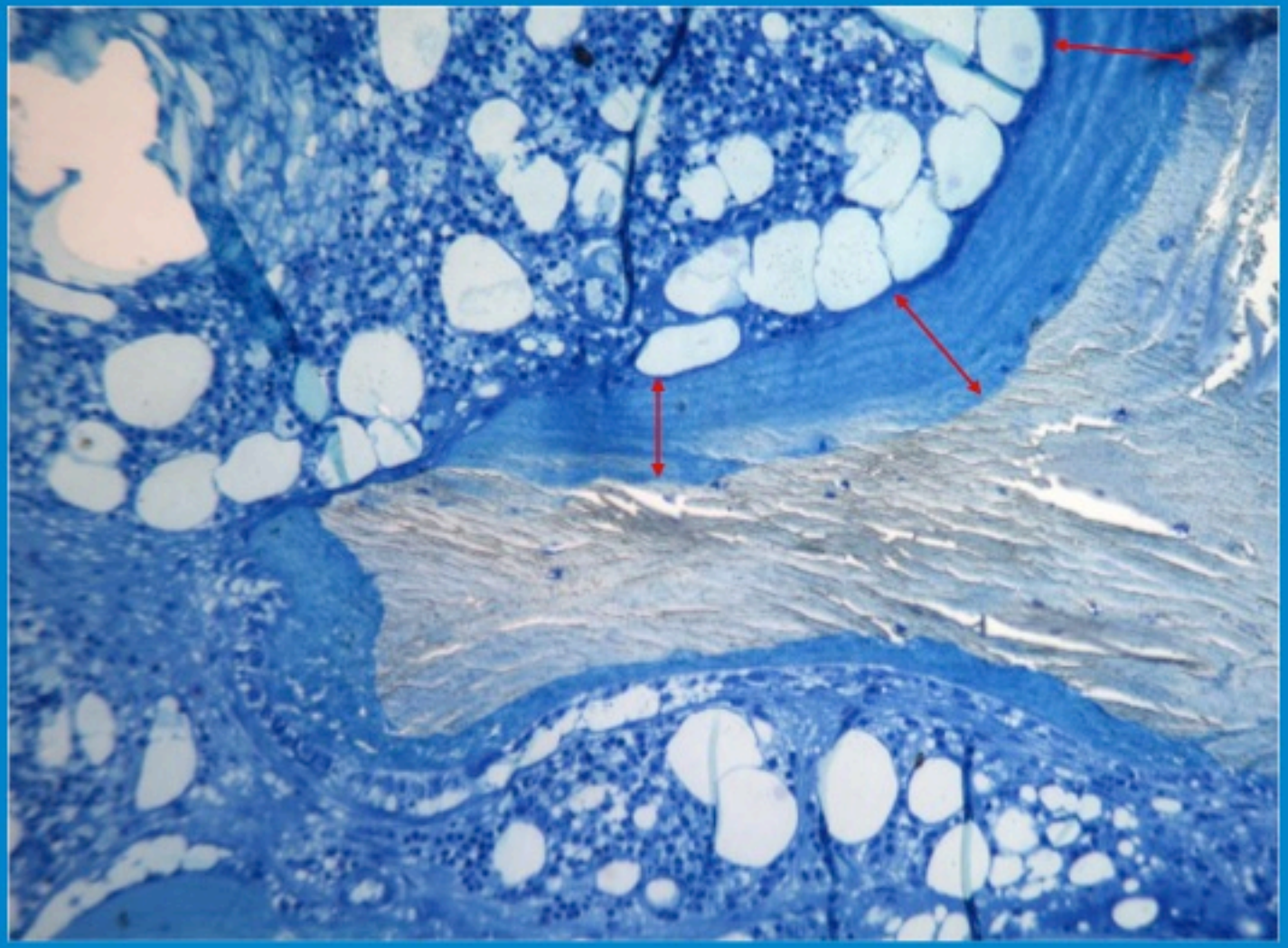


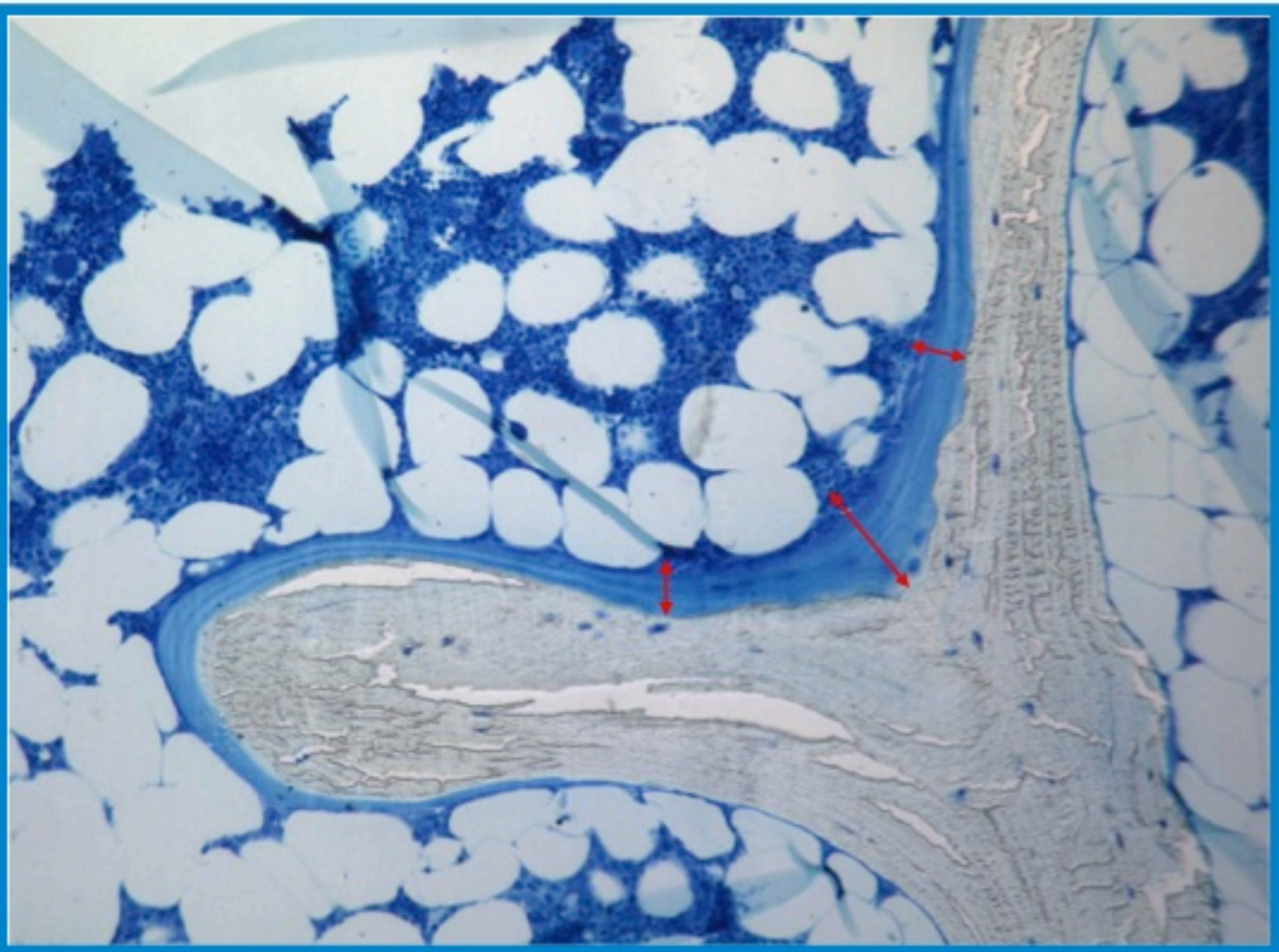
Figure 4 Pseudofracture (arrow) in the left os ilium in a patient with osteomalacia.

Severe vitamin D deficiency



Courtesy of P. Ballanti

Moderate vitamin D deficiency



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OMEOSTASI DEI FOSFATI

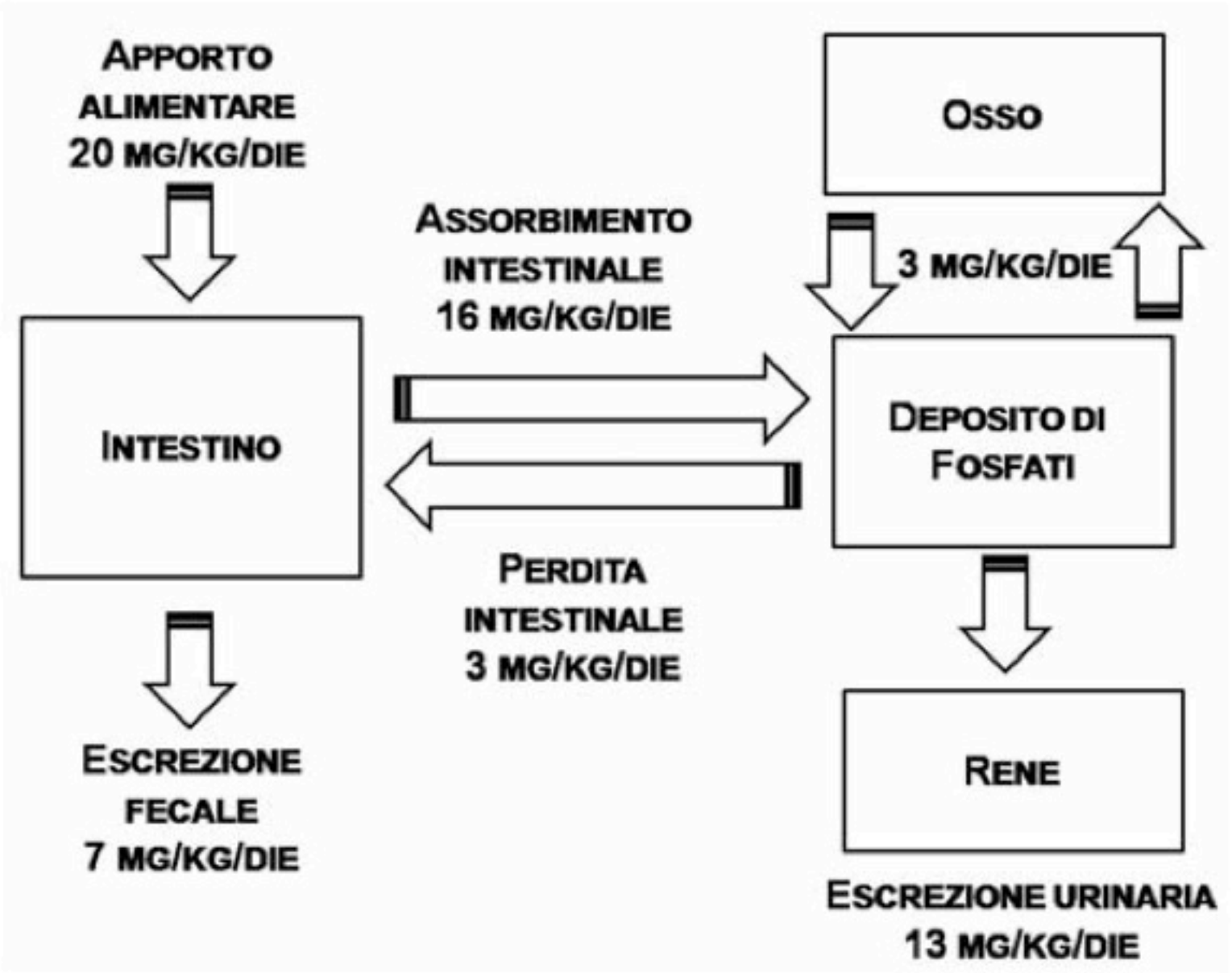

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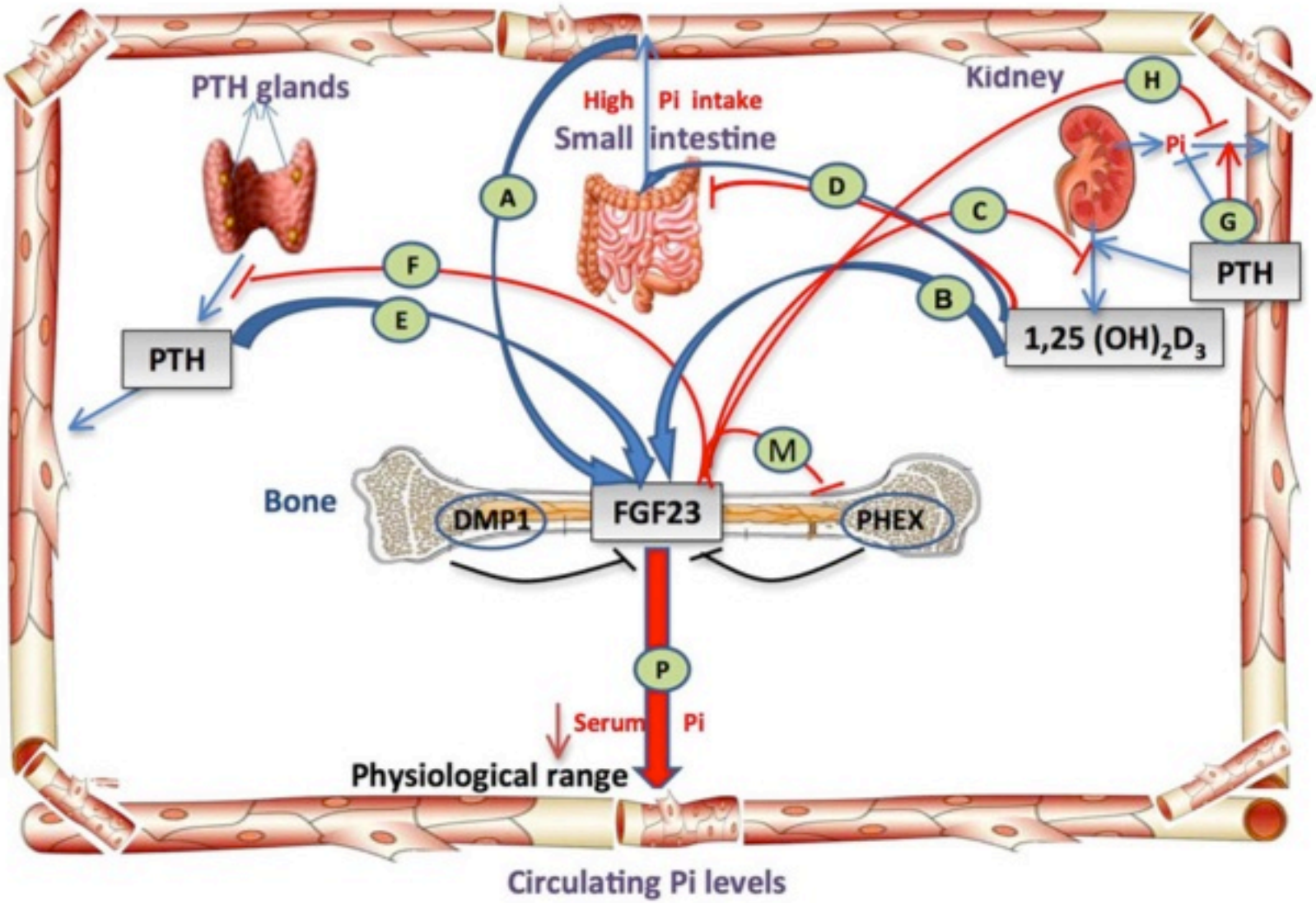
Table 1. Normative Values for Serum Phosphate by Age

Age (yr)	*Mean*	*2.5th percentile*	*97.5th percentile*
0–0.5	6.7 (2.15)	5.8 (1.88)	7.5 (2.42)
2	5.6 (1.81)	4.4 (1.43)	6.8 (2.20)
4	5.5 (1.77)	4.3 (1.38)	6.7 (2.15)
6	5.3 (1.72)	4.1 (1.33)	6.5 (2.11)
8	5.2 (1.67)	4.0 (1.29)	6.4 (2.06)
10	5.1 (1.63)	3.8 (1.24)	6.2 (2.01)
12	4.9 (1.58)	3.7 (1.19)	6.1 (1.97)
14	4.7 (1.53)	3.6 (1.15)	6.0 (1.92)
16	4.6 (1.49)	3.4 (1.10)	5.8 (1.88)
20	4.3 (1.39)	3.1 (1.01)	5.5 (1.78)
Adult	3.6 (1.15)	2.7 (0.87)	4.4 (1.41)

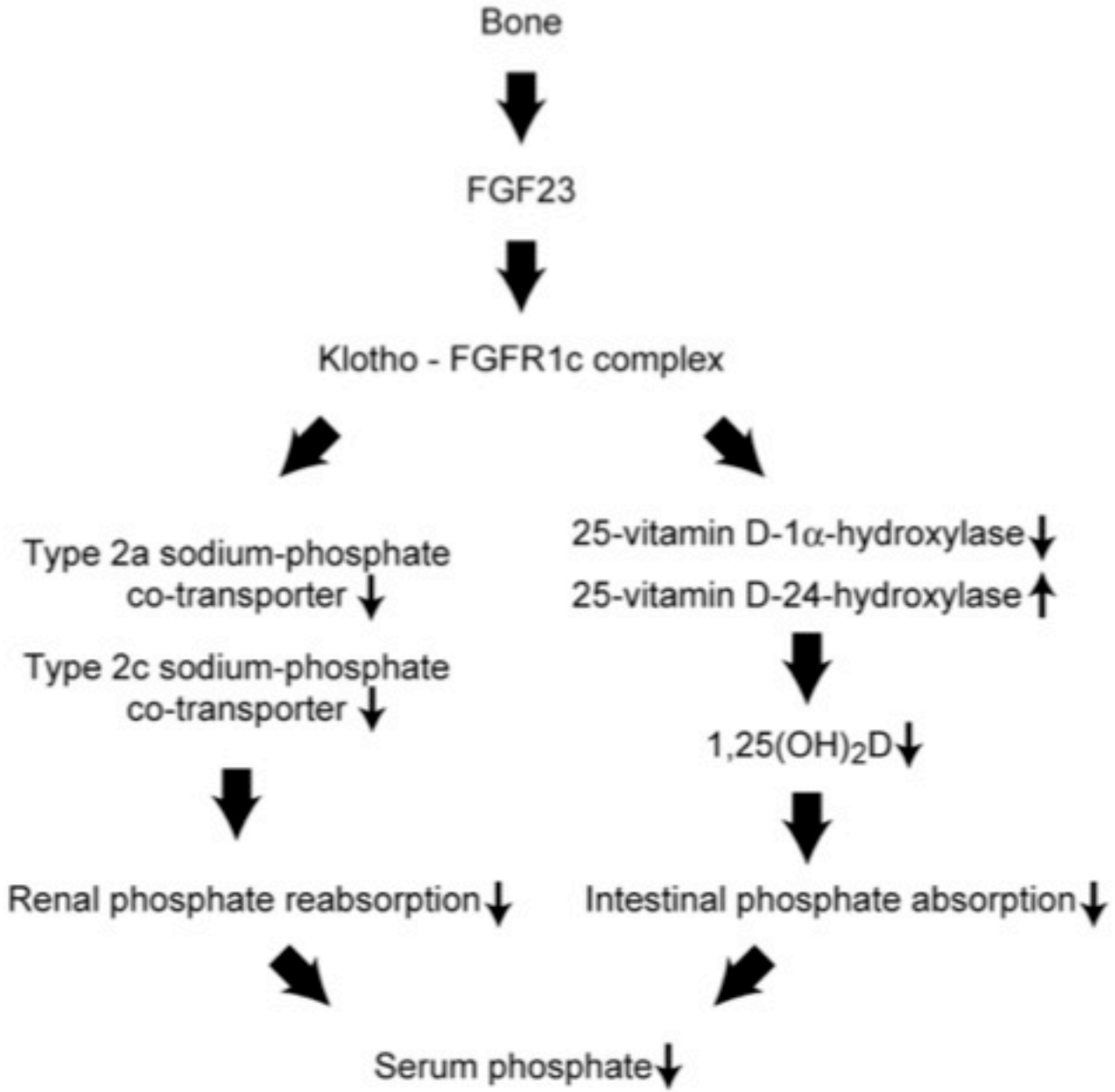
Values are shown as mg/dl and mM in parentheses.

Negative regulation of phosphate homeostasis by FGF23



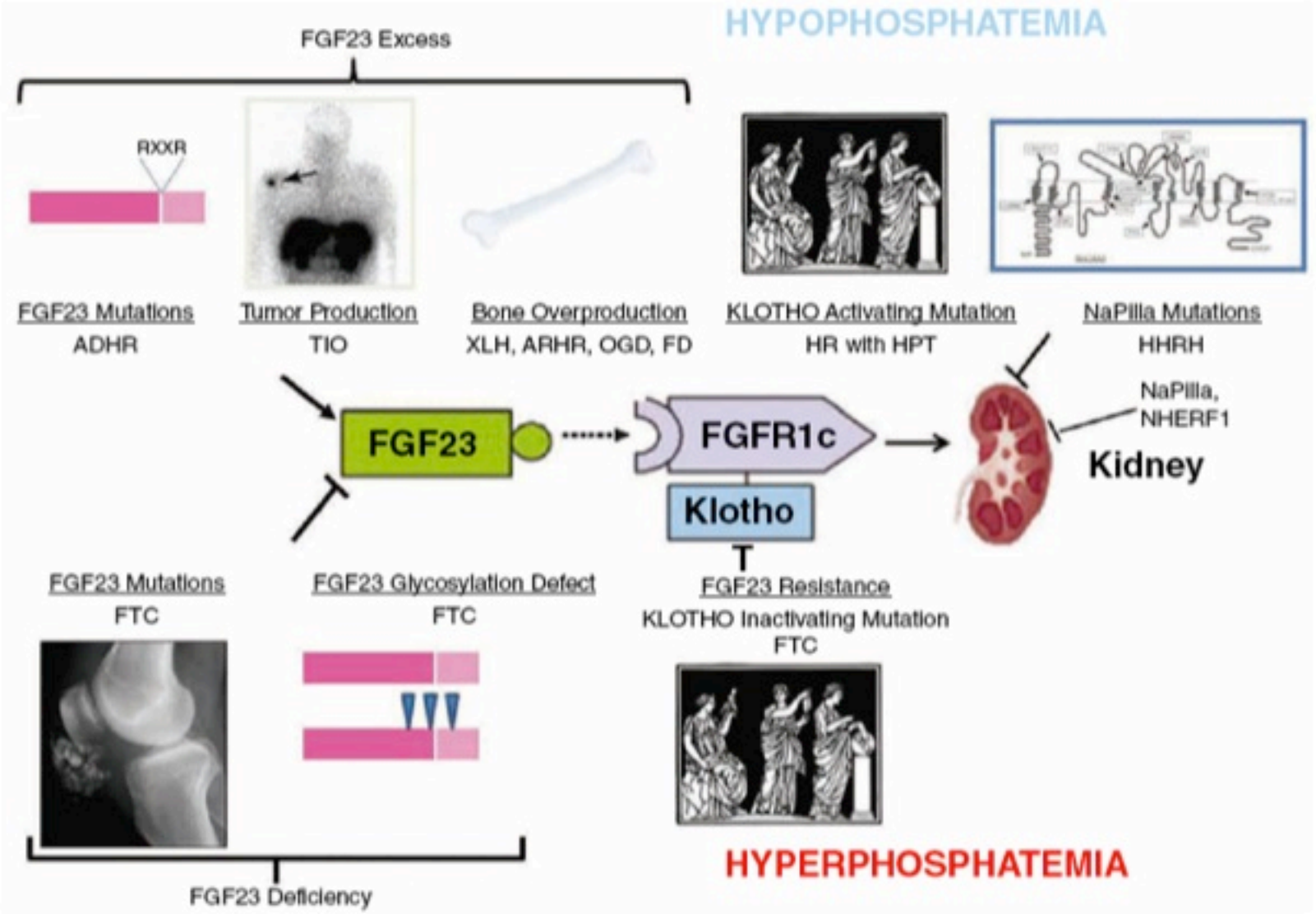
FGF23 action, or resultant action: ⊣ , →

Fukumoto S, IBMS BoneKEy. 2010



Fukumoto S, IBMS BoneKEy. 2010

Molecular mechanisms of disorders of phosphate homeostasis



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Characteristics of Renal Phosphate Wasting Disorders

Disease (OMIM)	Defect	Pathogenesis
TIO	Mesenchymal tumor	Ectopic, unregulated production of FGF23 and other phosphatonins sFRP4, MEPE, FGF7
XLH (307800)	*PHEX* mutation	Inappropriate FGF23 synthesis from bone
ADHR (193100	*FGF23* mutation	Increased circulating intact FGF23 caused by mutations that render it resistant to cleavage
HHRH (241530)	*SLC34A3* mutation	Loss of function NaPiIIc mutations that result in renal phosphate wasting without a defect in $1,25(OH)_2D_3$ synthesis
ARHR1 (241520)	*DMP1* mutation	Loss of DMP1 causes impaired osteocyte differentiation and increased production of FGF23
ARHR2 (613312)	*ENPP1* mutation	Increased production of FGF23
HR and HPT (612089)	*α-KLOTHO* translocation	Increased KLOTHO, FGF23, and downstream FGF23 signaling
Fibrous dysplasia (139320)	*GNAS* mutation	Increased FGF23 production from the dysplastic bone
Linear nevus sebaceous syndrome	Excess FGF23 production	Increased FGF23 production from the dysplastic bone and from the nevi
OGD (166250)	*FGFR1* mutation	Increased FGF23 production from the dysplastic bone
NPHLOP1 (612286)	*SLC34A1* mutation	Renal phosphate wasting without a defect in $1,25(OH)_2D_3$ synthesis
NPHLOP2 (612287)	*SLC9A3R1* mutation	Renal phosphate wasting through potentiation of PTH-mediated cAMP production
FRTS2 (613388)	*SLC34A1* mutation	Renal phosphate wasting without a defect in $1,25(OH)_2D_3$ synthesis

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Figure 2

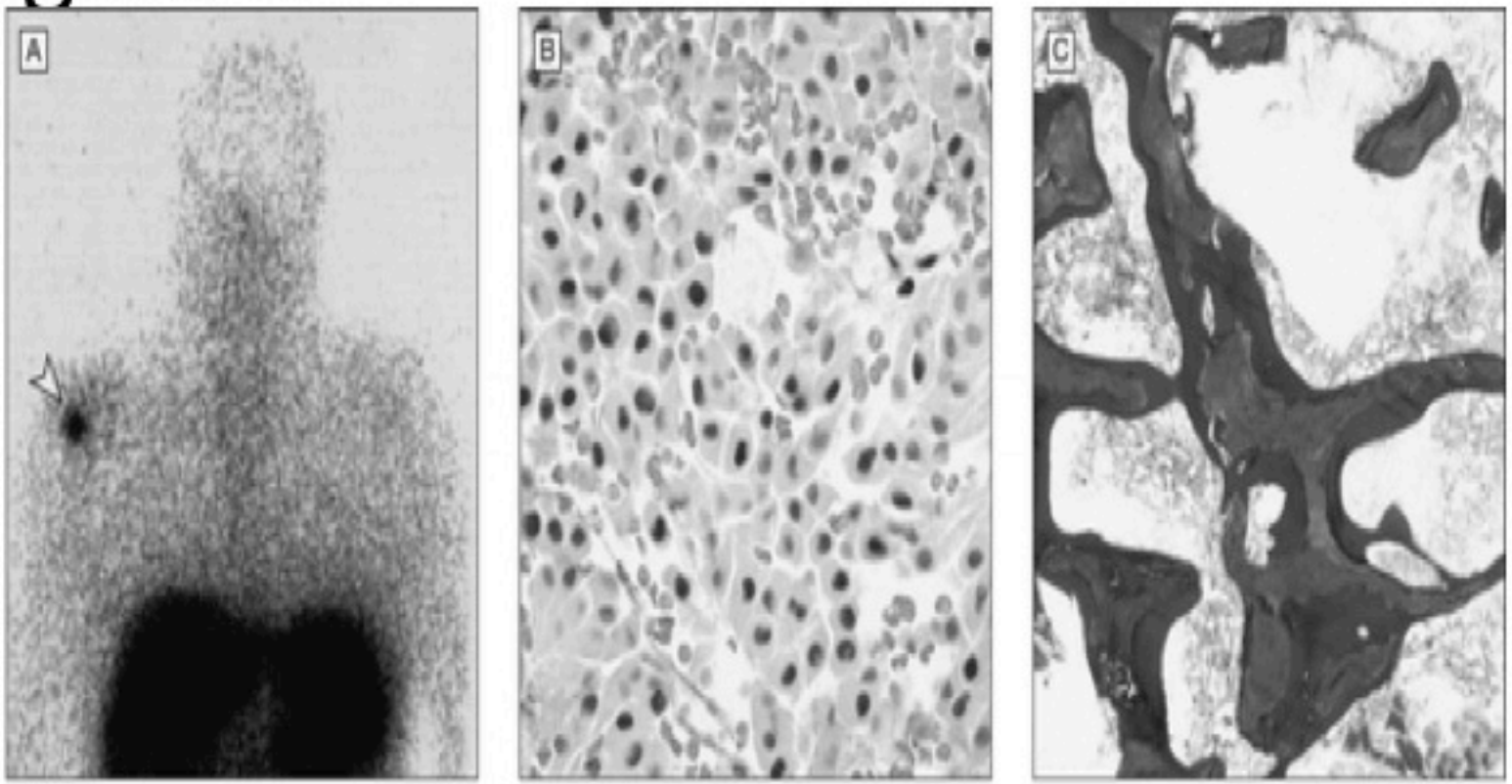

Figure 2 Radiographic and histologic features in TIO. (A) Octreotide scan showing small mesenchymal tumor in the head of the humerus. (B) Hemiangiopericytoma with with numerous pericytes and vascular channels (H&E strain). (C) Bone biopsy with Goldner stain. Excessive osteoid or unmineralized bone matrix composed mainly of collagen stains pink. Minerlized bone stains blue. This bone biopsy shows severe osteomalacia.

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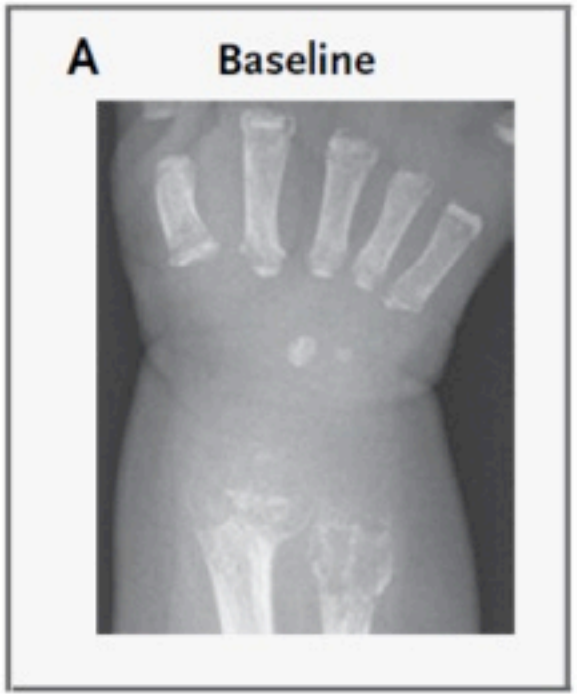
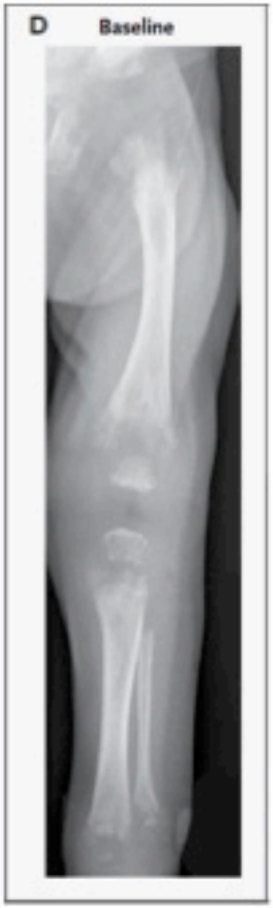
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

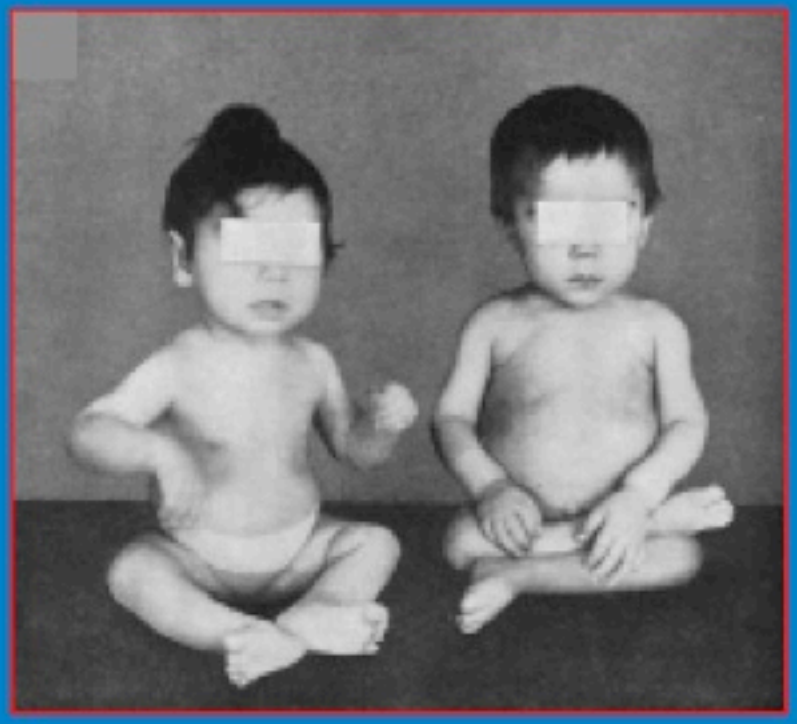
Enzyme-Replacement Therapy in Life-Threatening Hypophosphatasia



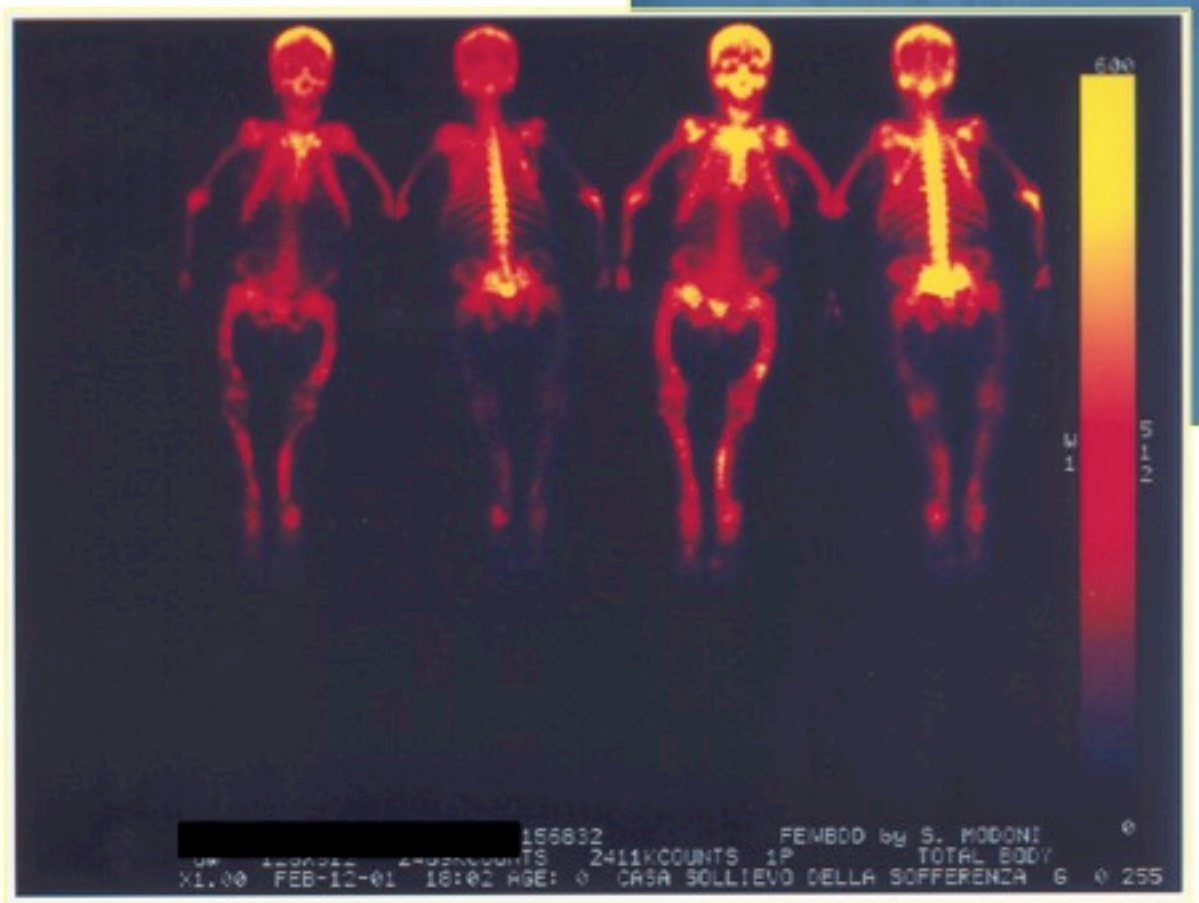


Whyte MP et al, 2012

Skeletal deformities observed in rickets



Eliot E.M., and Park E.A. 1938. Rickets. In: *Brennemann's practice of pediatrics*. Volume 1. W.F. Prior Company Inc. Hagerstown, Maryland, USA. 1-110.


[redacted]156832
FEWBOD by S. MODONI
2411KCOUNTS 1P
TOTAL BODY
X1.00 FEB-12-01 18:02 AGE: 0 CASA SOLLIEVO DELLA SOFFERENZA 6 0 255