X-linked Hypophosphataemic Rickets

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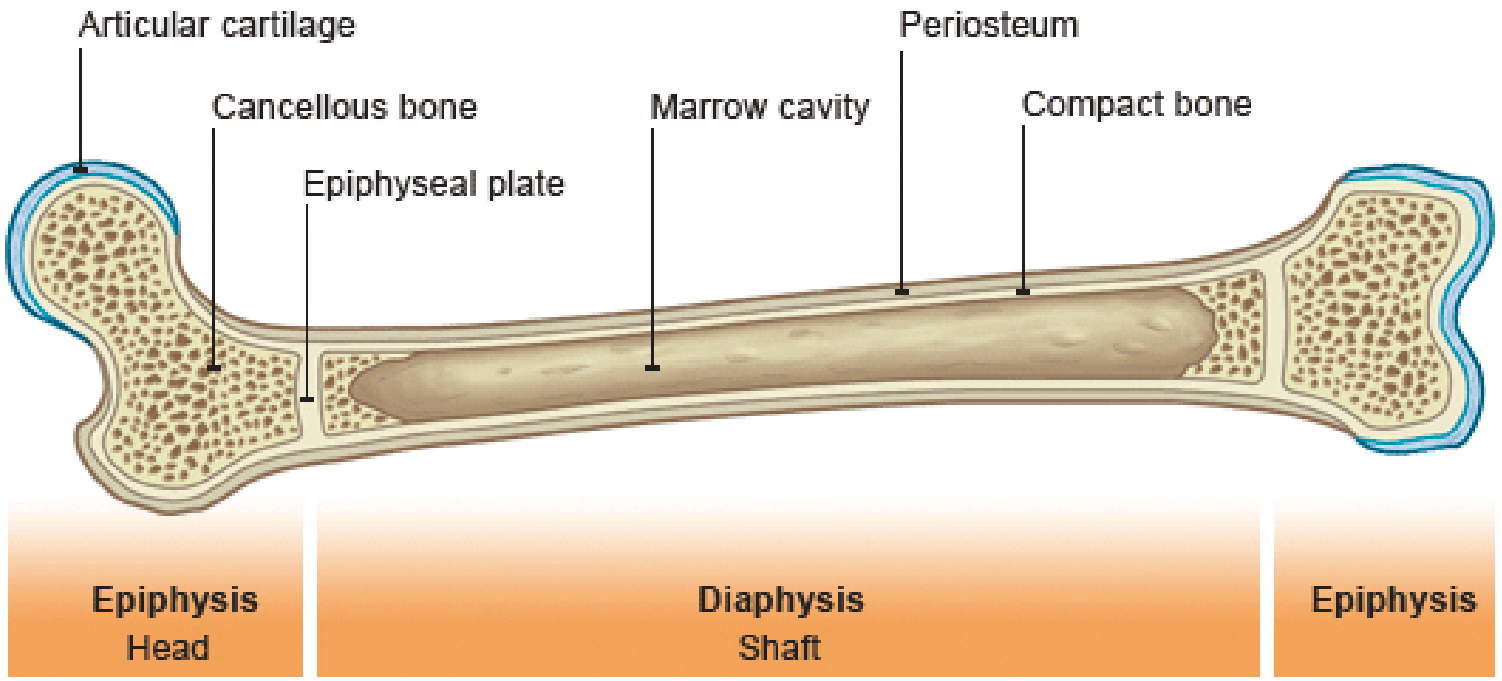
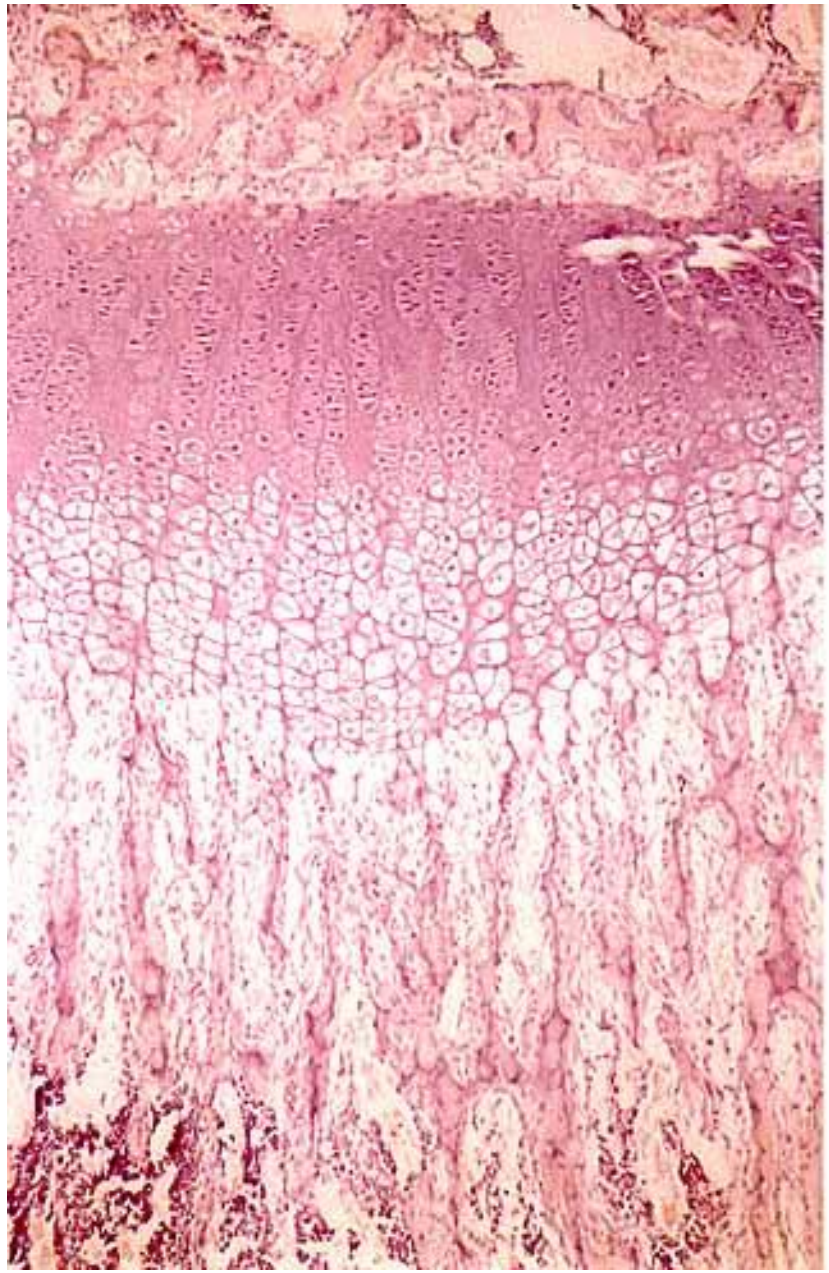
What is rickets?

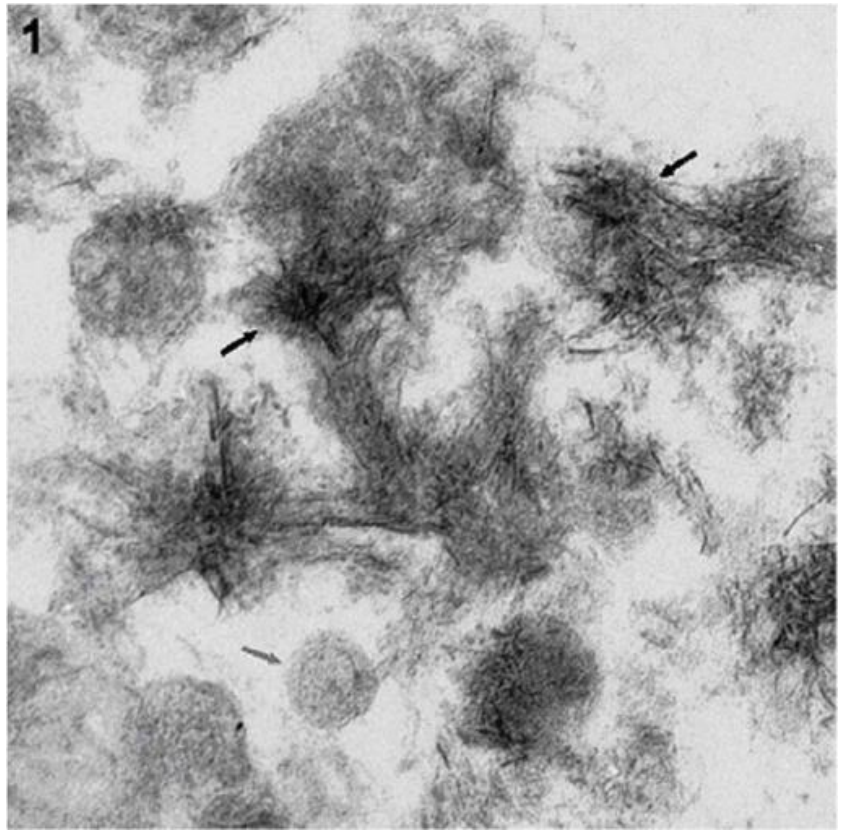
- Failure to mineralise newly-formed bone
- Increase in growth plate hypertrophic chondrocyte cell layer

Bones – general structure

- Cortex
- Trabeculae
- Growth plate
- Modelling
- Remodelling




Resting zone
Proliferating zone
Hypertrophic zone
Ossification zone
Trabecular bone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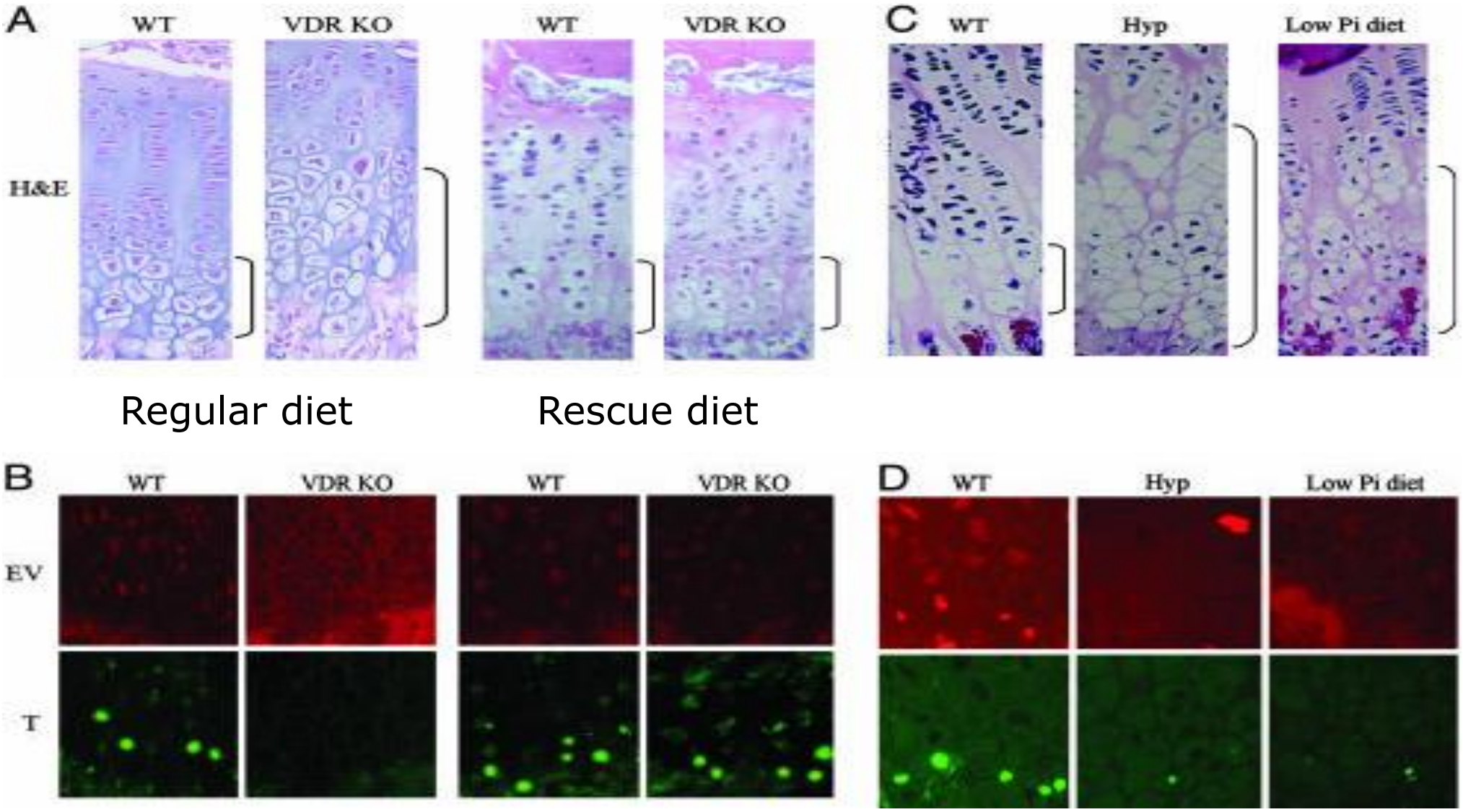
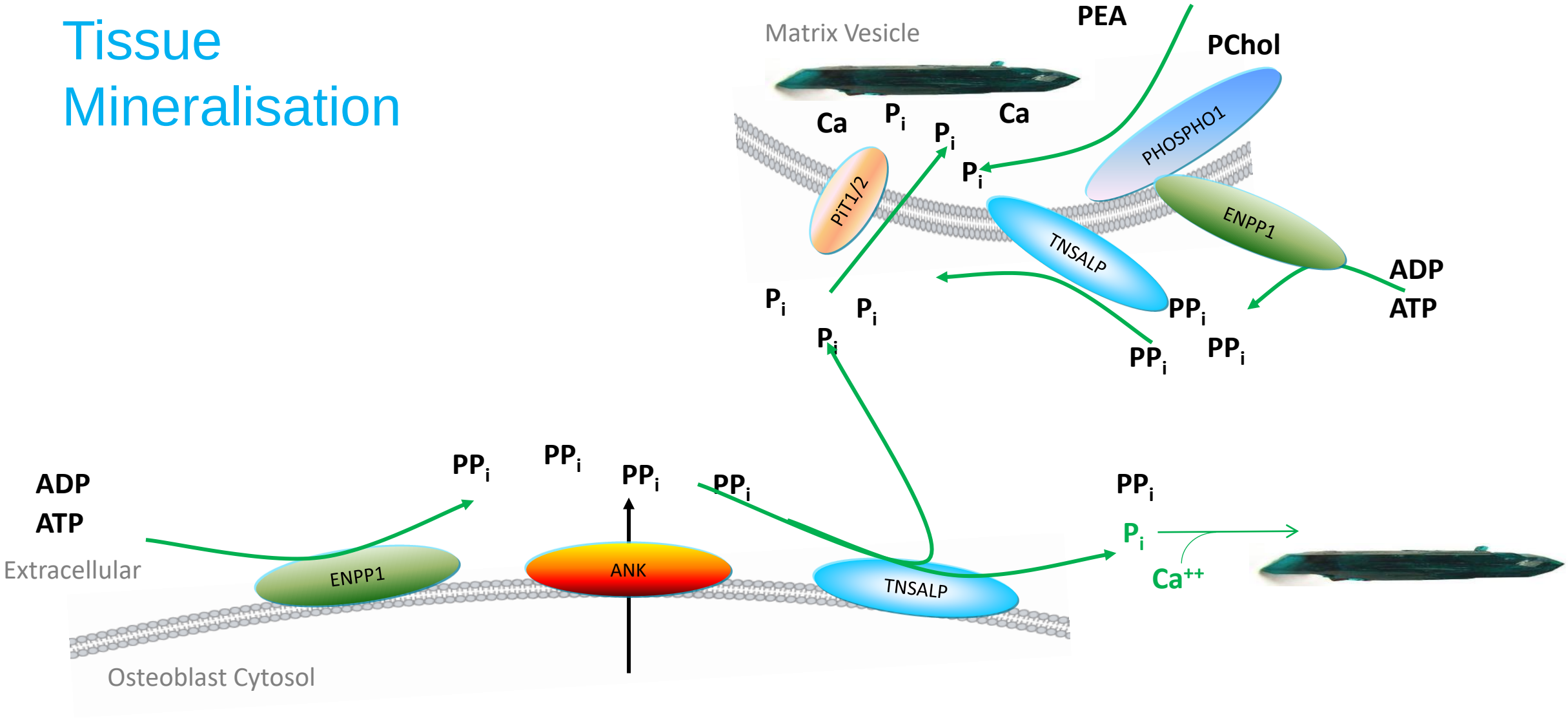
Rachitic mouse growth plates

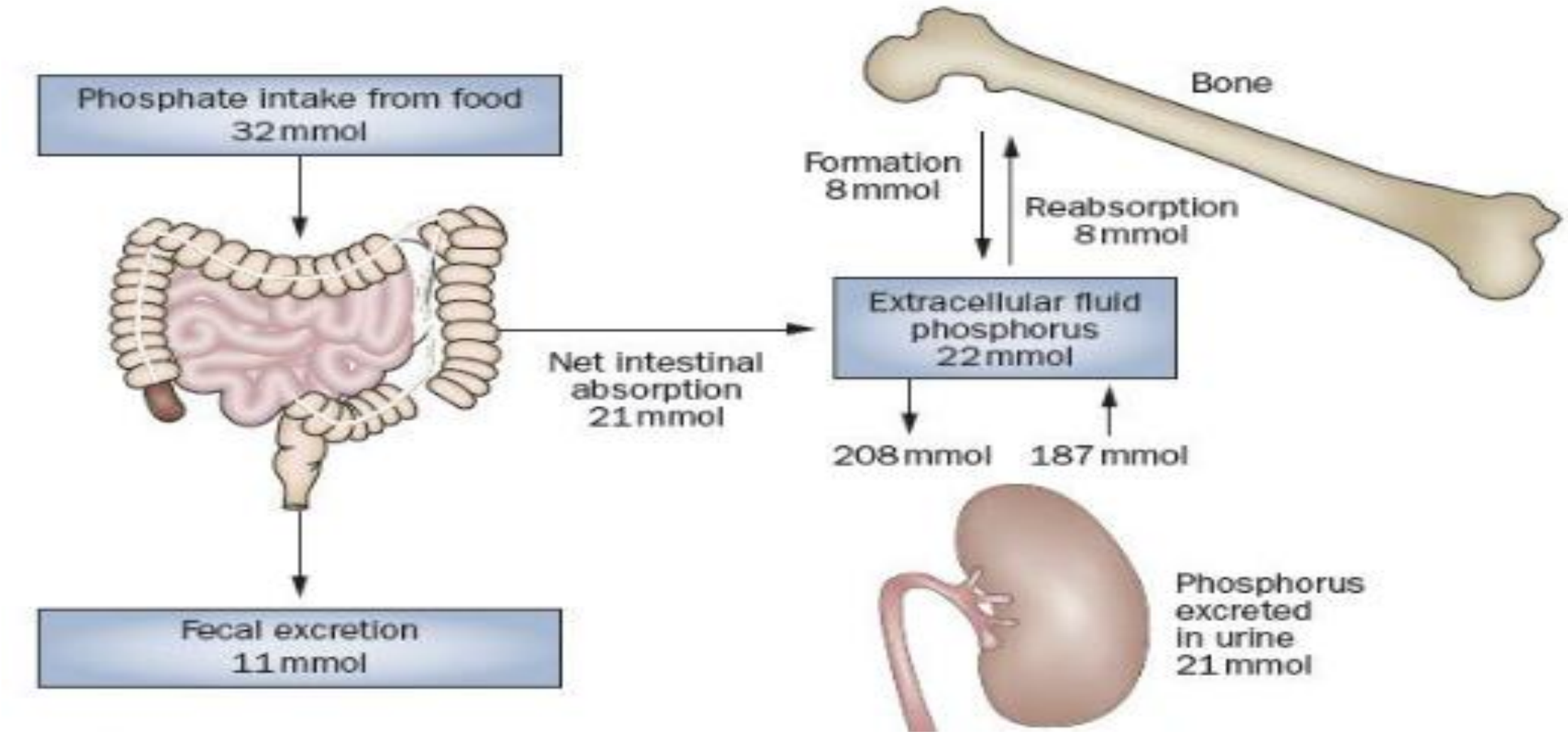


Sabbagh et al Proc Natl Acad Sci U S A. 2005 July 5; 102(27): 9637–9642

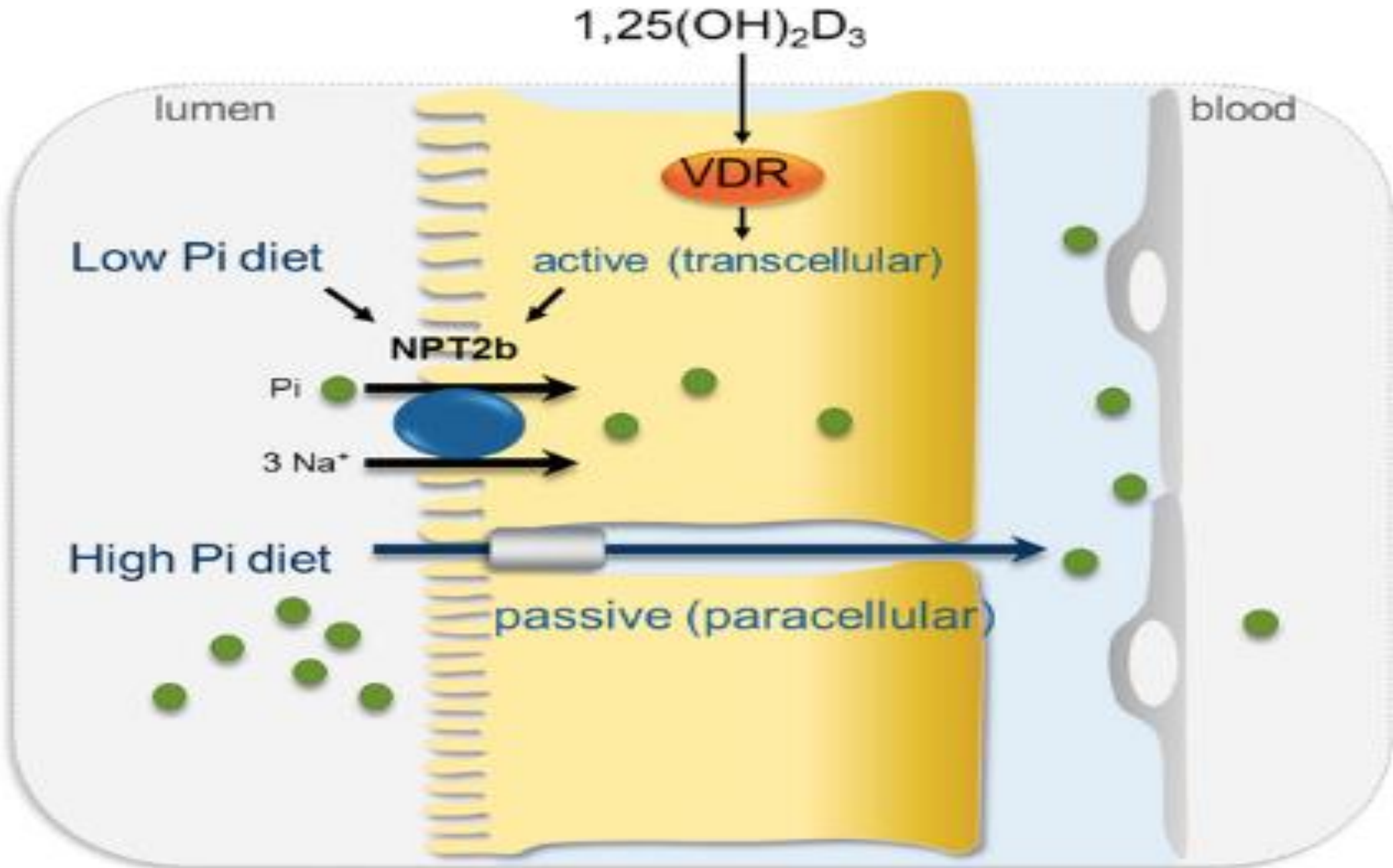
Tissue Mineralisation



Phosphate



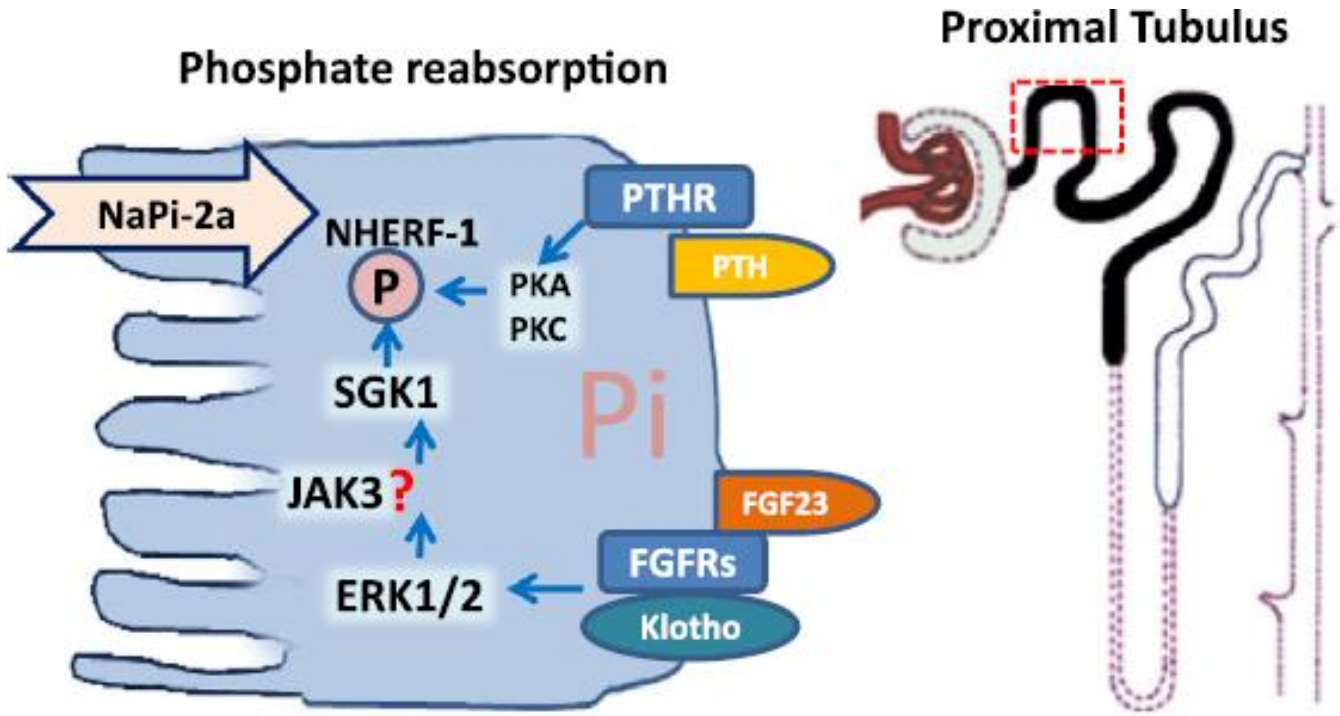
Naderi A. doi:10.1038/nrneph.2010.121



Christakos S et al. doi:10.1038/bonekey.2013.230

Phosphate excretion

- 60-70% reabsorption in PCT
- NaPi2a and NaPi2c
- PTH
- FGF23
- NHERF-1
- FGFR1, 3 and 4



FGF23-Klotho signaling axis in the kidney

Reinhold G. Erben *, Olena Andrukhova

XLH – history

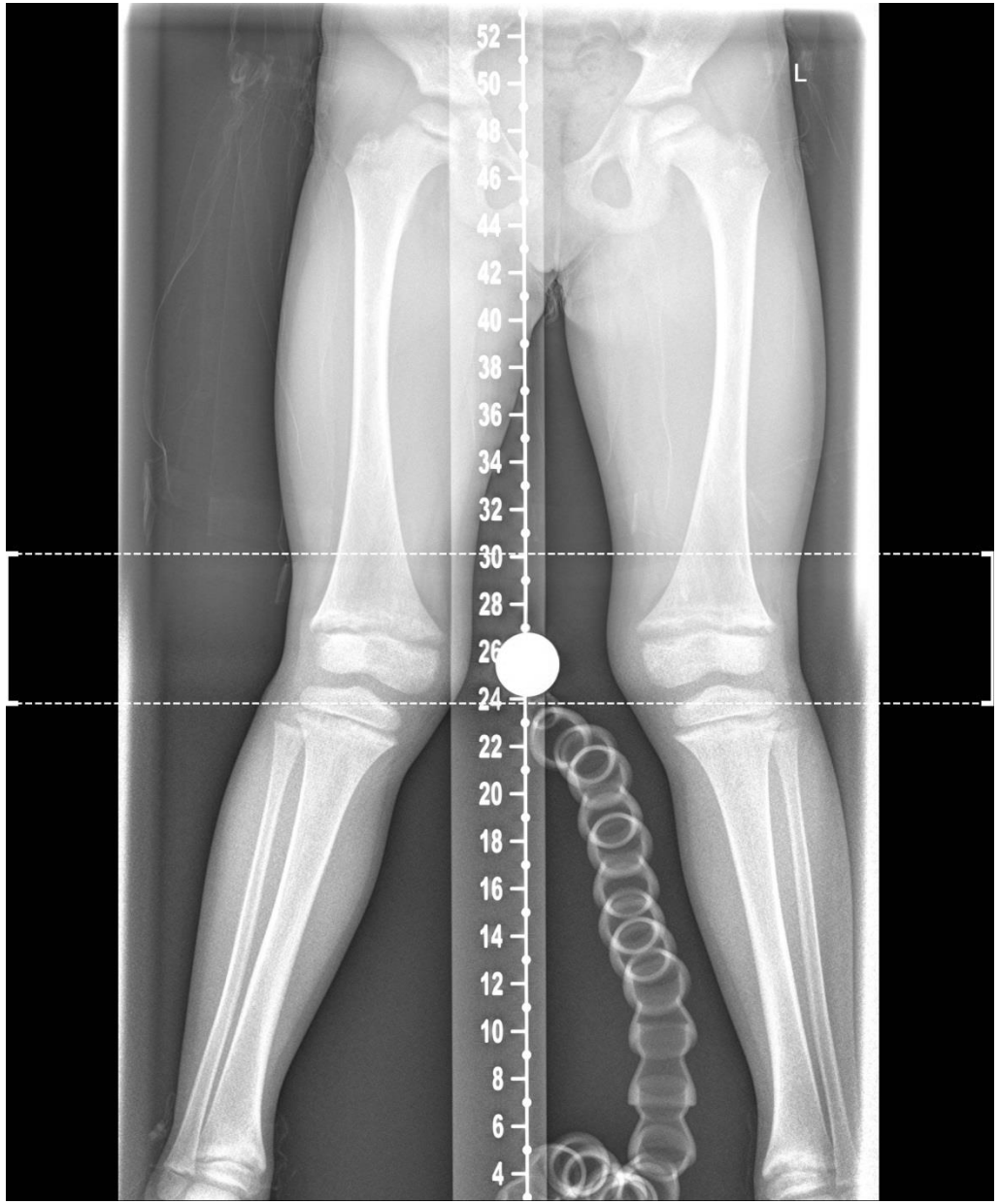
- 1937 Albright – VDRR
- 1940 Christensen – familial
- 1958 Winters – X-linked dominant
- 1976 Eicher – HYP mouse
- 1985 Harrell – use of calcitriol to heal osteomalacia
- 1986 Read – short arm X chromosome
- 1987 Thakker – Xp22
- 1995 Francis – P(H)EX
- 2000 Econs – FGF23 in ADHR

XLH - diagnosis

- Clinical
- Imaging
- Biochemical
- Genetic

XLH – clinical manifestations 1

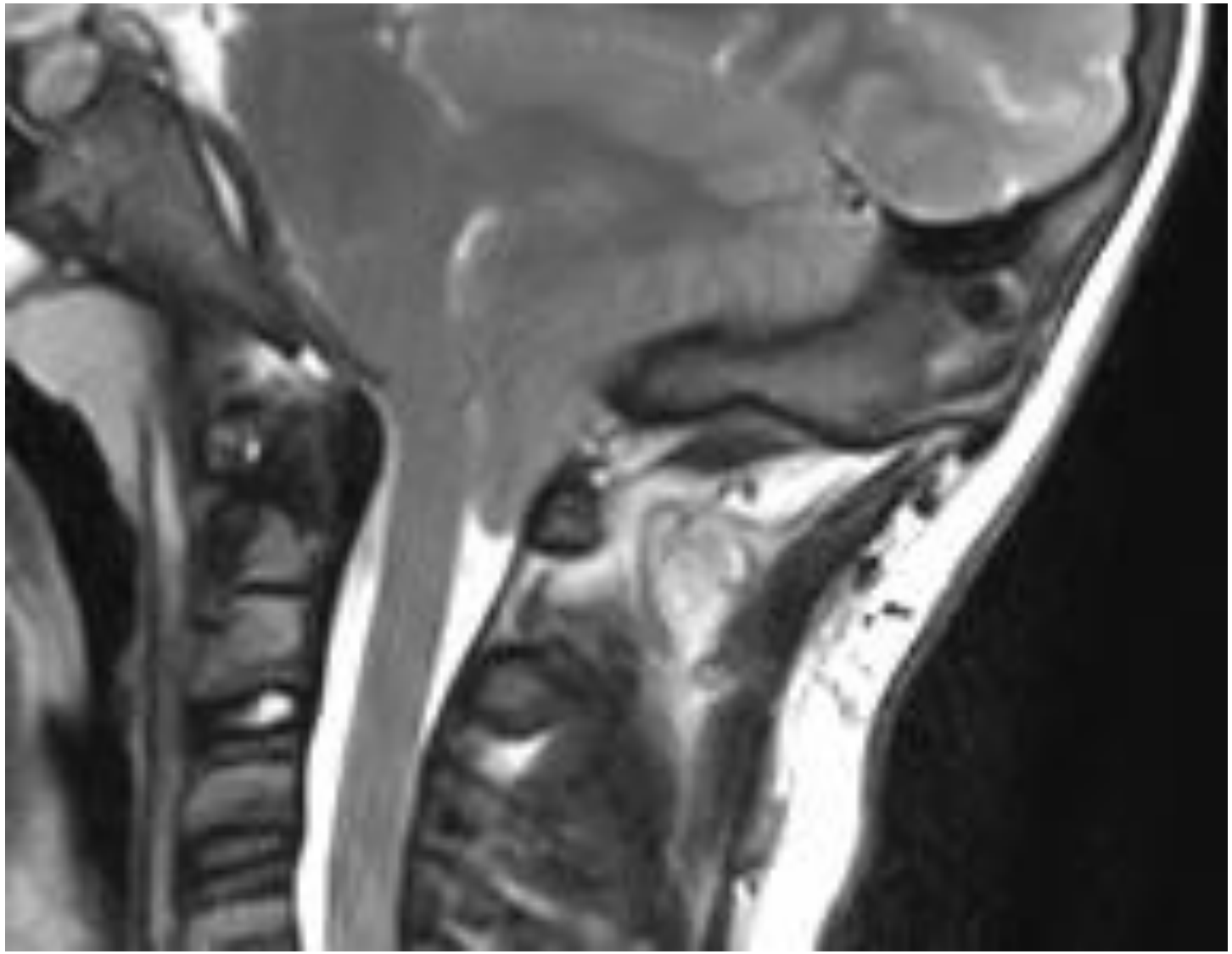
- Long bones
  - Rickets
  - Deformity
  - Short stature
- Slight delay puberty
  - PHV 13 and 15 yrs girls and boys, respectively



Images provided by Paul Arundel

XLH – clinical manifestation 2

- Skull
  - Craniosynostosis (75%)
  - Chiari type 1 (48% tonsillar herniation)
  - Syringomyelia (>16%)
- Teeth
  - Abscess – 61.5% adults with Hx 5 or more cf 5% with 1 in general population
  - Periodontitis
- Myopathy
- Enthesopathy
- Osteoarthropathy



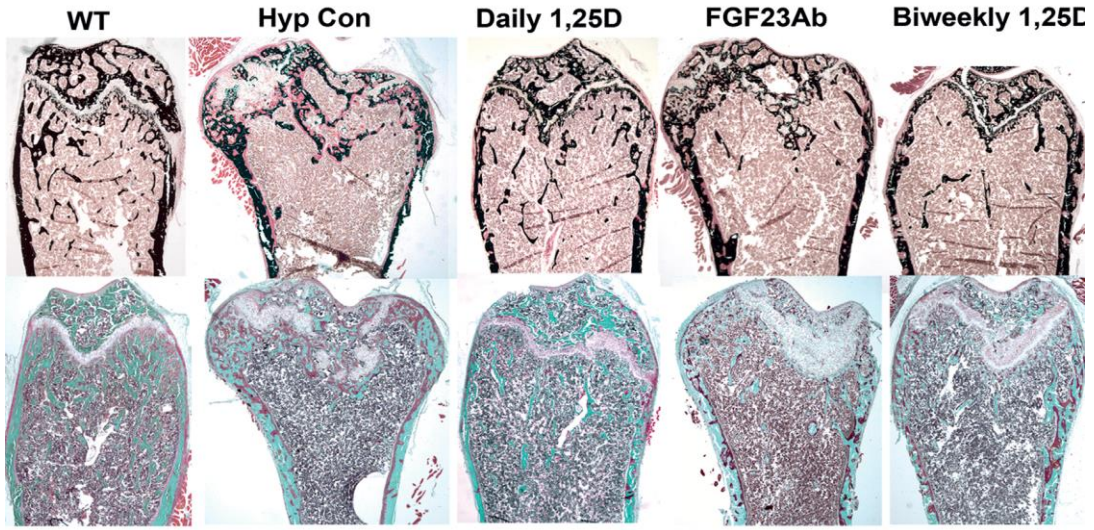
Images provided by Paul Arundel

XLH – history of treatment

- High dose vitamin D (1937)
  - Toxicity risk
- Phosphate and vitamin D (1972)
  - Growth plate effect
- Phosphate and activated vitamin D (1980)
- Activated vitamin D alone?

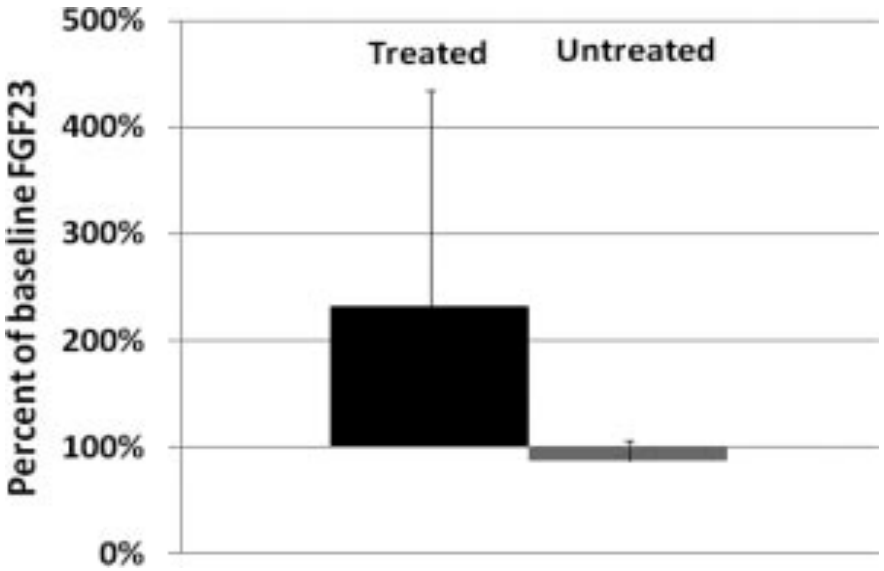
1,25-Dihydroxyvitamin D Alone Improves Skeletal Growth, Microarchitecture, and Strength in a Murine Model of XLH, Despite Enhanced FGF23 Expression

Eva S Liu,[1,2,3] Janaina S Martins,[2,3,4] Adalbert Raimann,[2,3,5] Byongsoo Timothy Chae,[2] Daniel J Brooks,[2,6] Vanda Jorgetti,[4] Mary L Bouxsein,[2,3,6] and Marie B Demay[2,3]



XLH – “traditional” medical management

- General approach
  - Phosphate
  - Activated form of vitamin D
- Monitoring for side-effects
- Other effects of treatment
  - PTH
  - FGF23

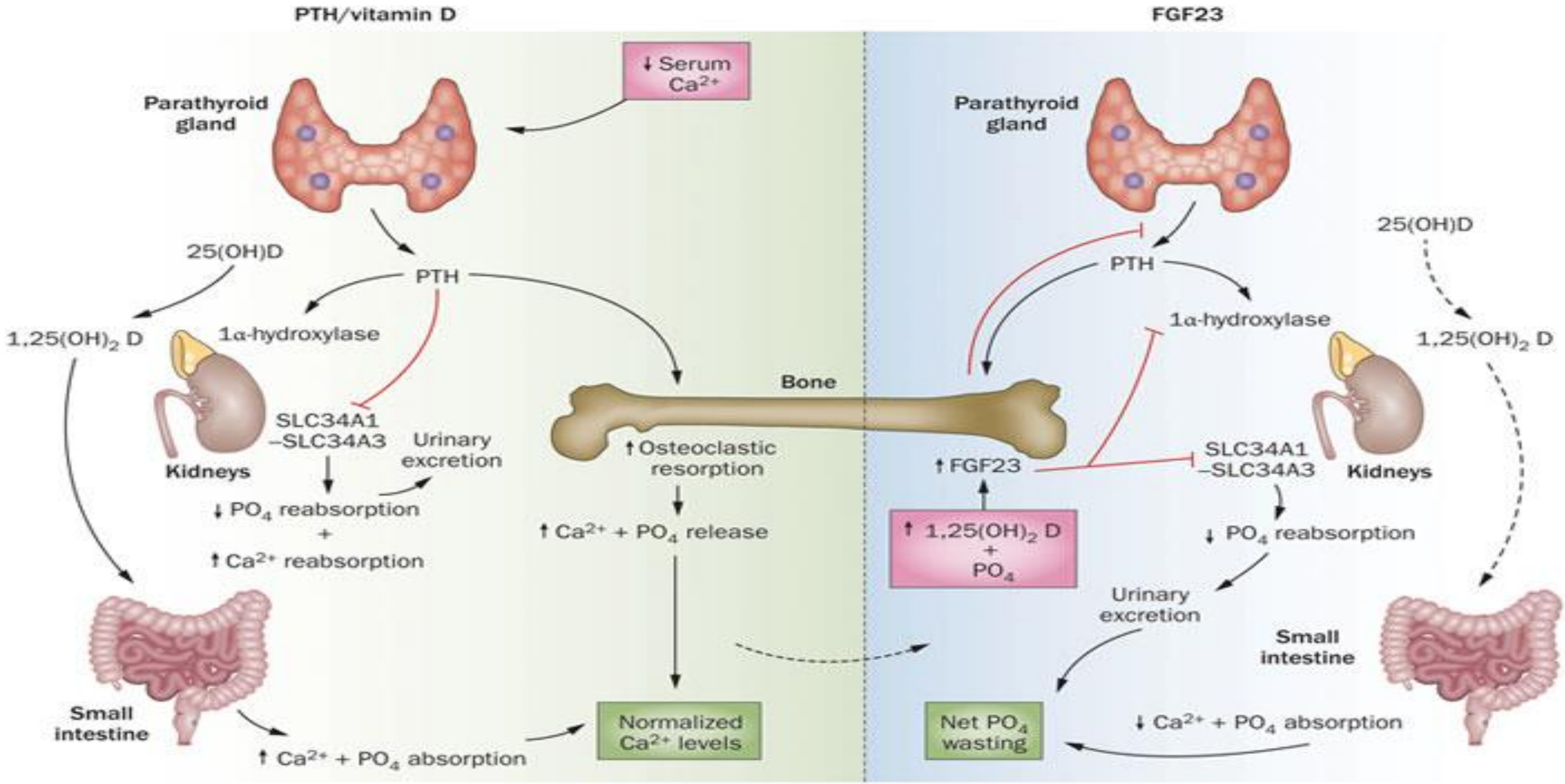


Treatment of X-Linked Hypophosphatemia with Calcitriol and Phosphate Increases Circulating Fibroblast Growth Factor 23 Concentrations

Erik A. Imel, Linda A. DiMeglio, Siu L. Hui, Thomas O. Carpenter, and Michael J. Econs

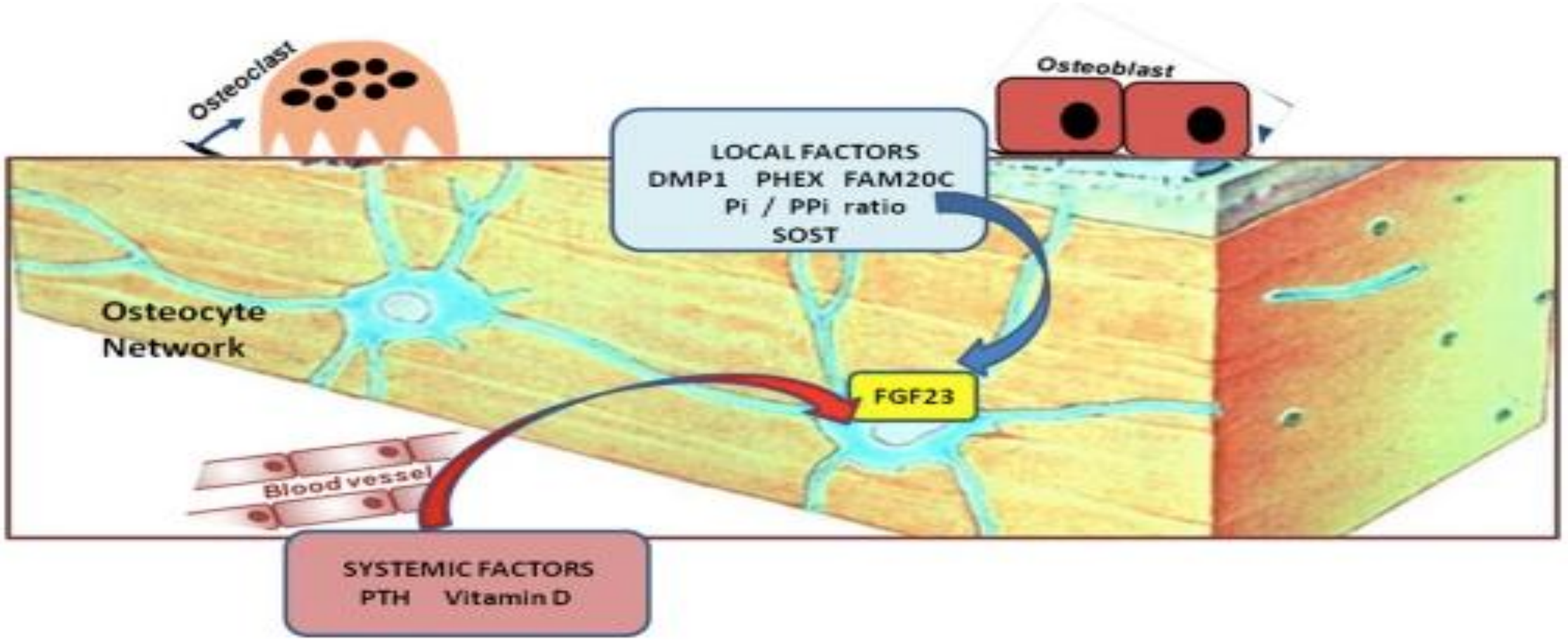
XLH – current surgical management

- Guided growth
- Osteotomy
- Cranial surgery



DiGirolamo D. DOI: 10.1038/nrrheum.2012.157

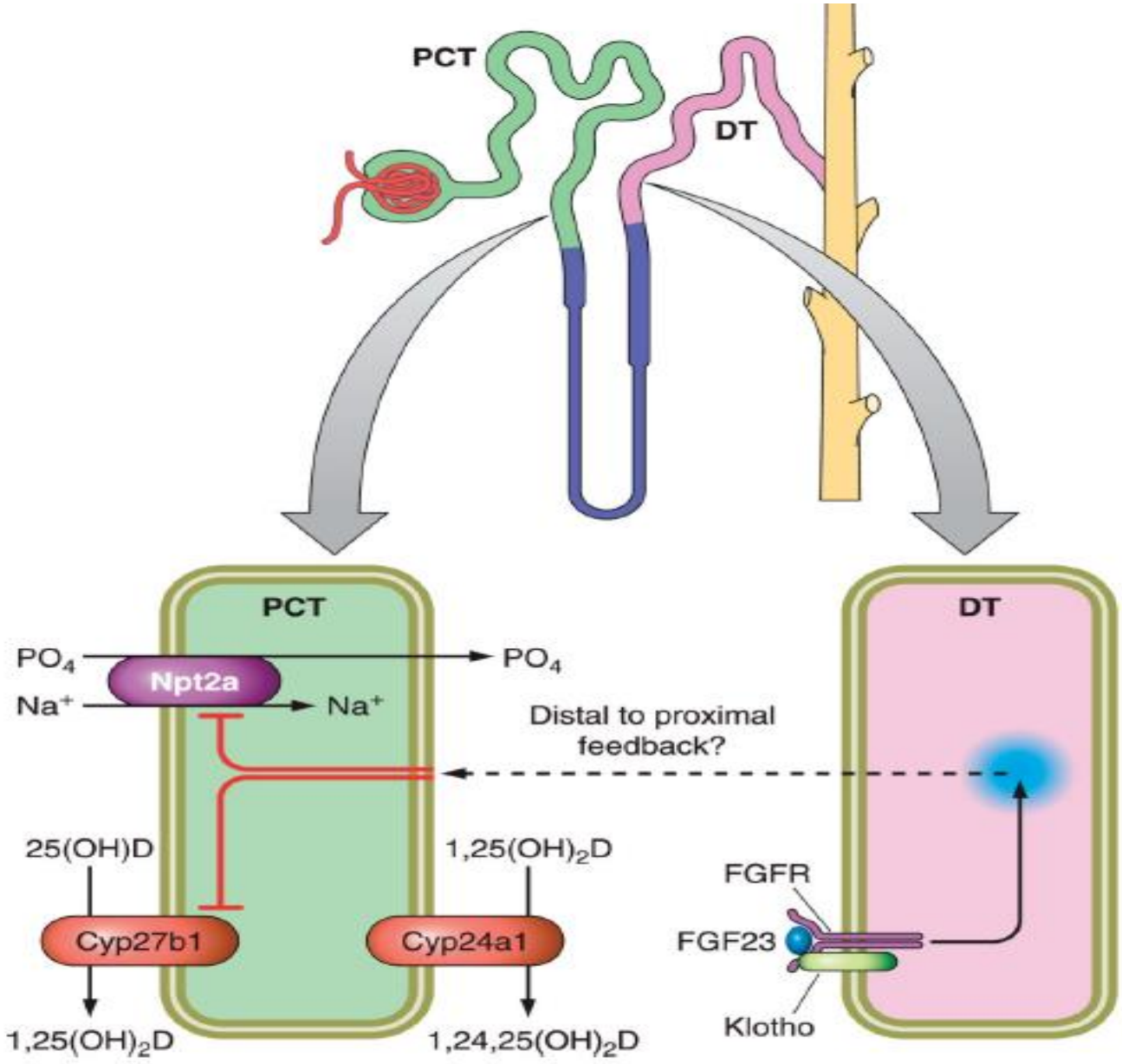
FGF23 in bone



Sapir-Koren R. DOI: 10.1002/biof.1186

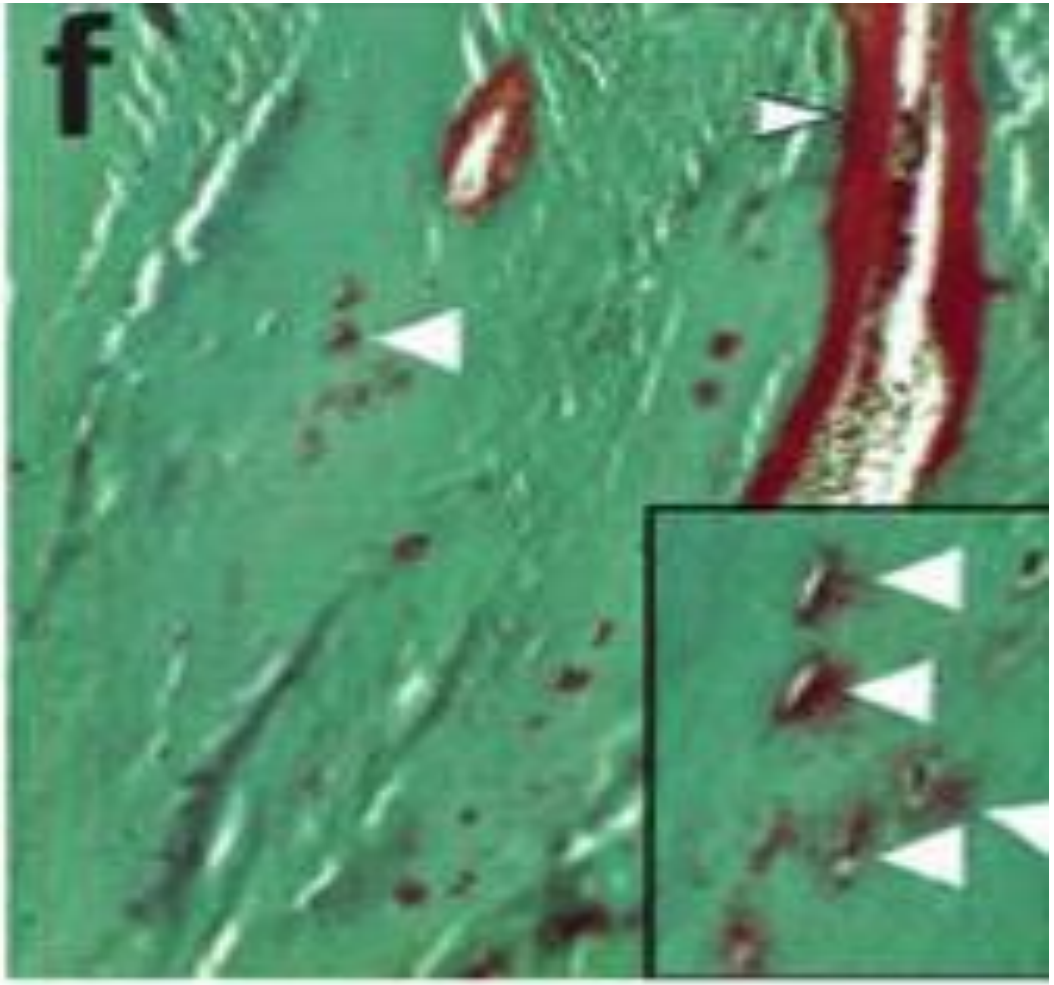
FGF23

- Hormone produced by osteoblasts and osteocytes
- Regulated by:
  - 1,25 OH_2 vitamin D
  - PTH
  - PHEX (local)
  - Mineralisation



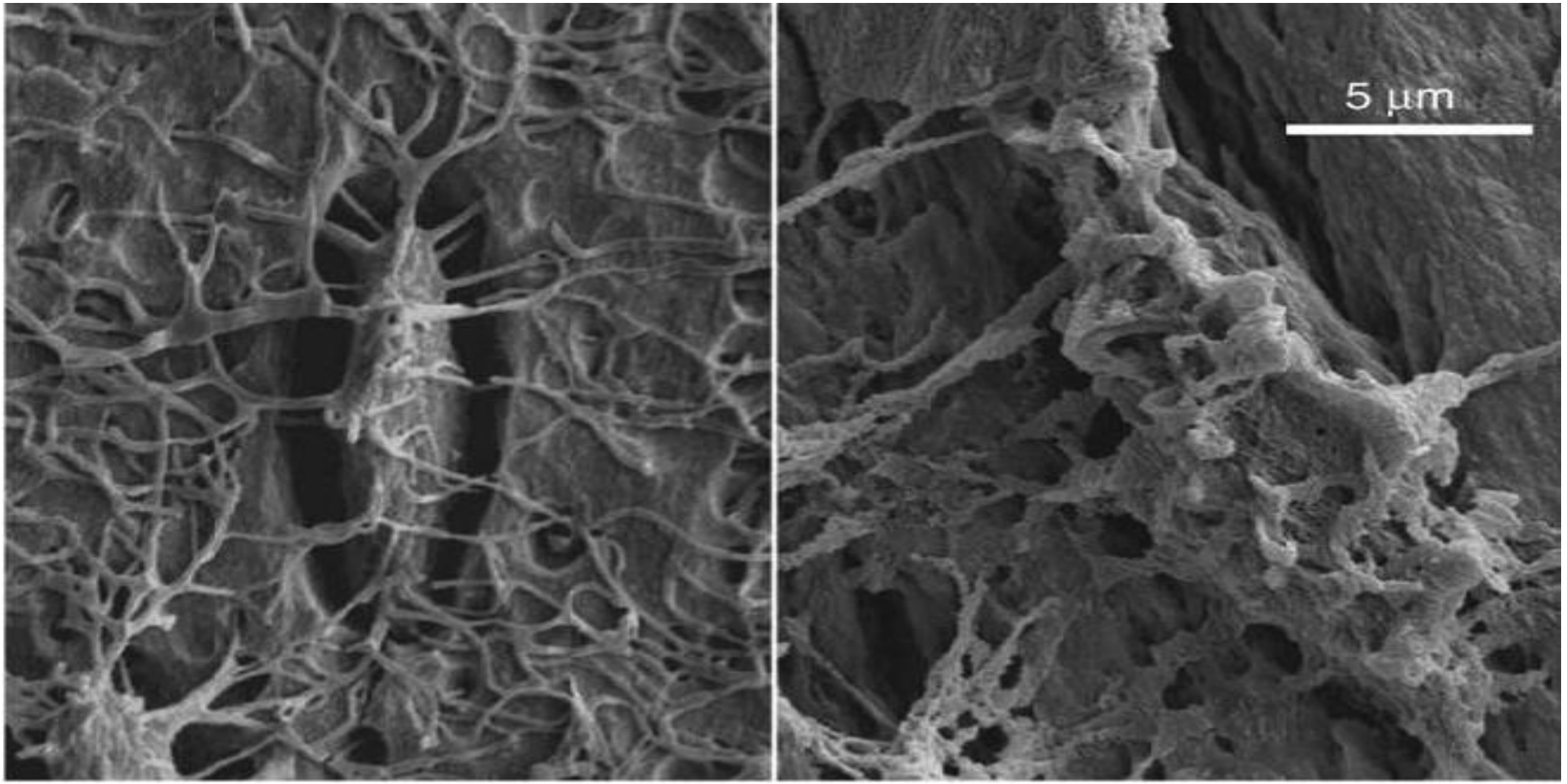
Martin A. DOI: 10.1152/physrev.00002.2011

ARHR



Feng JQ et al. Nature Genetics 2006;38:1310-5

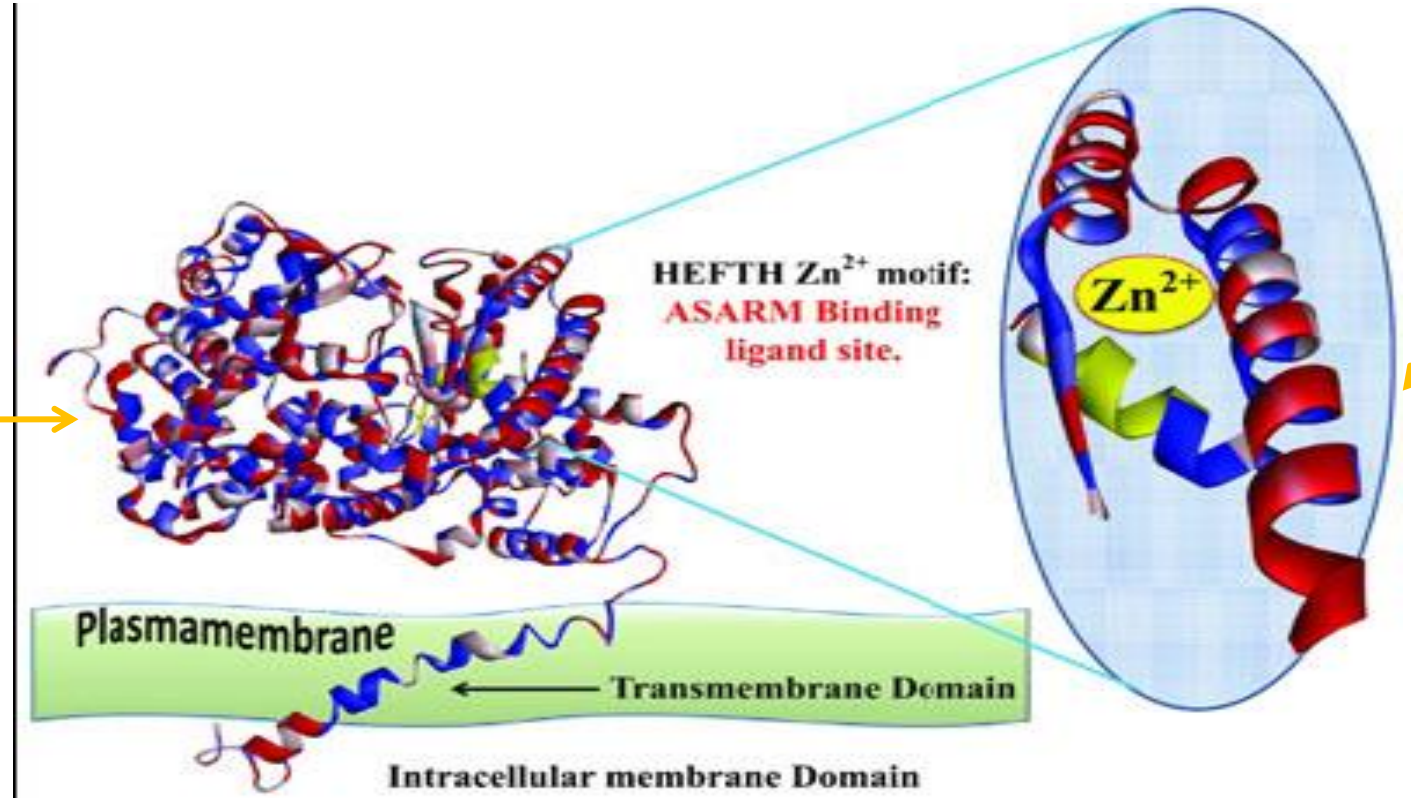
DMP1 -/- osteocytes



Feng JQ et al. Nature Genetics 2006;38:1310-5

PHEX and DMP1 - ASARM

PHEX



ASARM: peptide or motif

May compete for binding to PHEX

ASARM = Acidic Serine Aspartate-Rich MEPE

Rowe P. DOI: 10.1002/cbf.2841

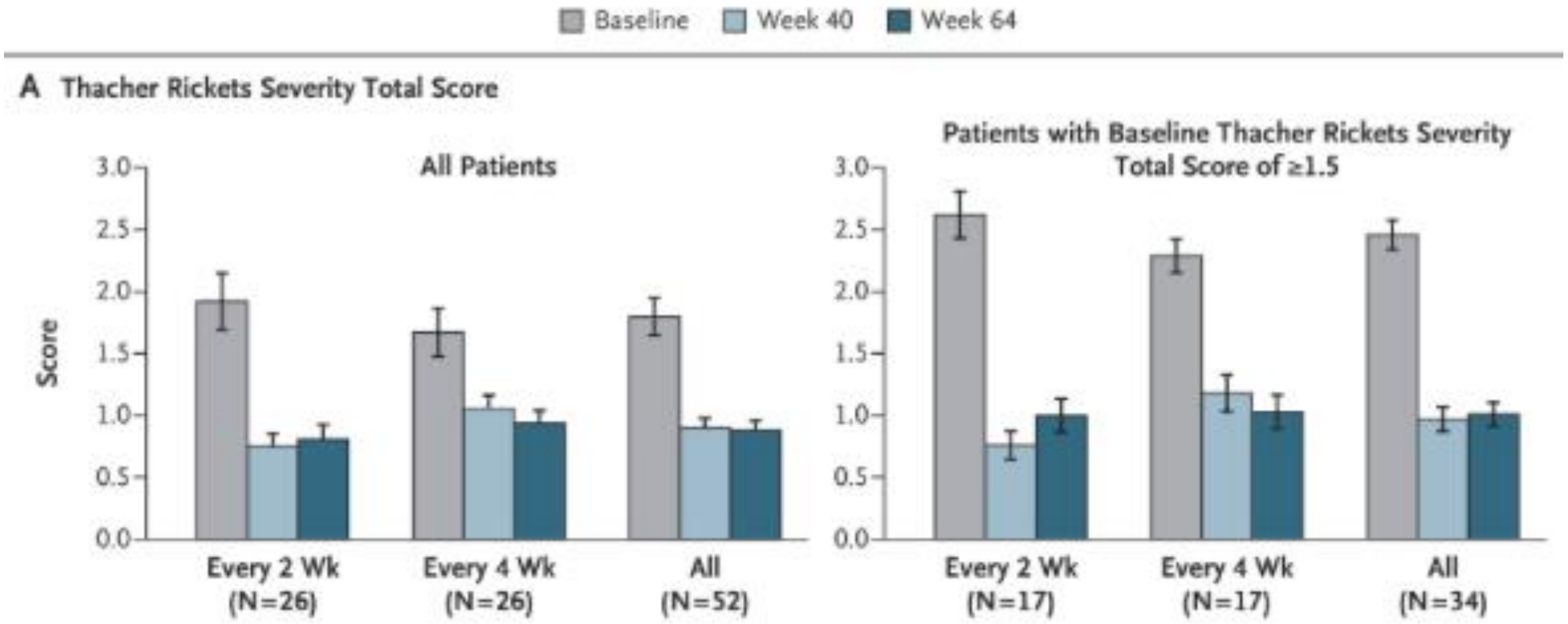
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Burosumab Therapy in Children with X-Linked Hypophosphatemia

Thomas O. Carpenter, M.D., Michael P. Whyte, M.D., Erik A. Imel, M.D., Annemieke M. Boot, M.D., Ph.D., Wolfgang Högler, M.D., Agnès Linglart, M.D., Ph.D., Raja Padidela, M.D., William van't Hoff, M.D., Meng Mao, Ph.D., Chao-Yin Chen, Ph.D., Alison Skrinar, Ph.D., Emil Kakkis, M.D., Ph.D., Javier San Martin, M.D., and Anthony A. Portale, M.D.

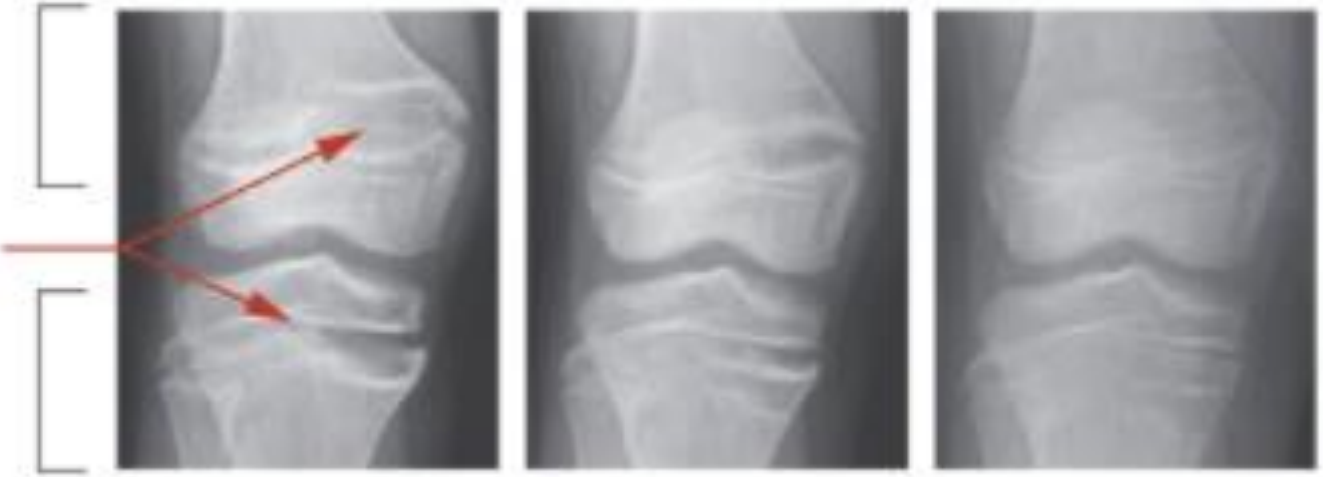
Change in rickets severity with burosumab



Carpenter *et al. N Engl J Med* 2018;378:1987-98

Exemplar radiographic change

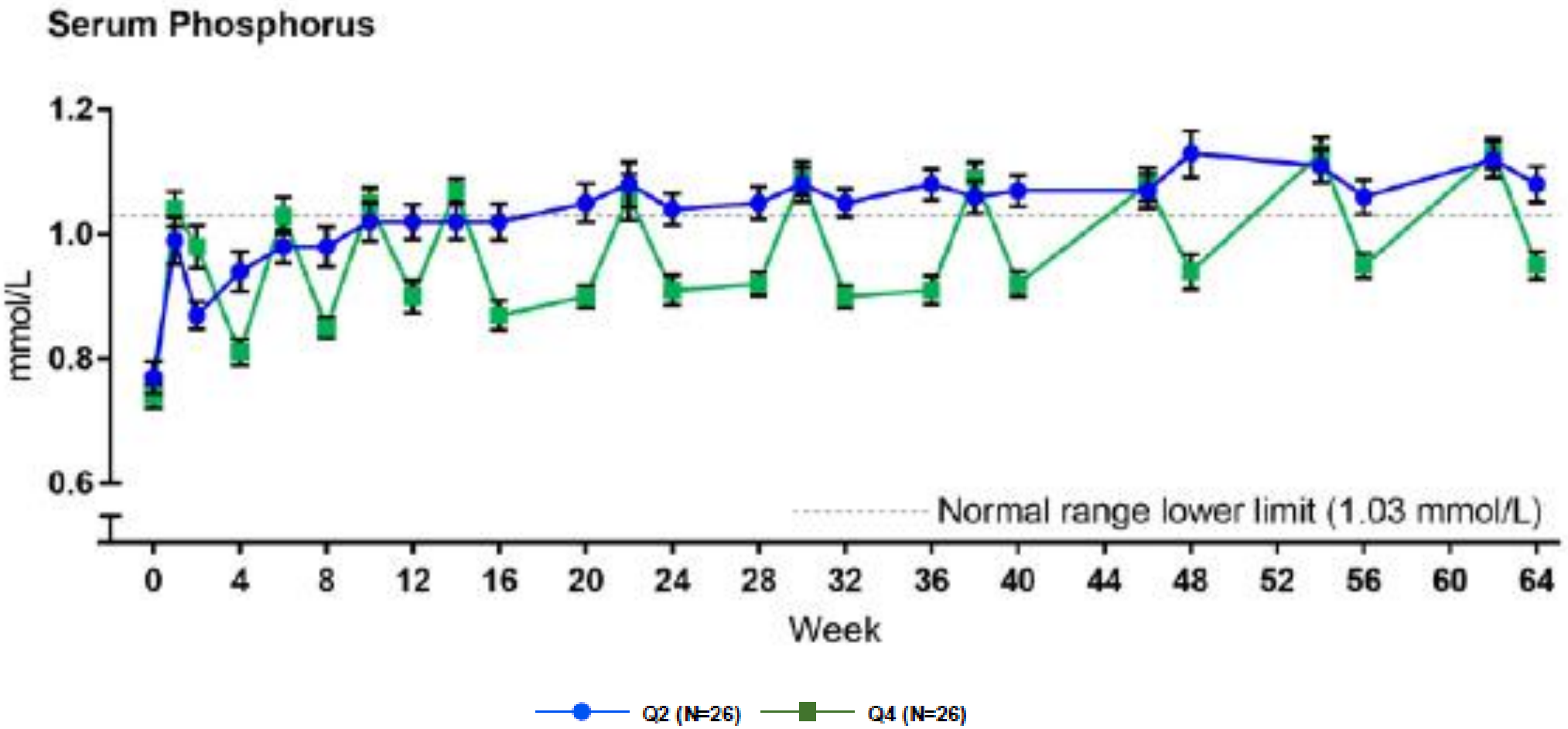
C Radiographs of the Knee in an 11-Year-Old Girl



	Baseline	Wk 40	Wk 64
Thacher Rickets Severity Knee Score	2.0	1.0	0.0
Radiographic Global Impression of Change Global Score		2.0	2.3

Carpenter *et al. N Engl J Med* 2018;378:1987-98

Improved serum phosphorus



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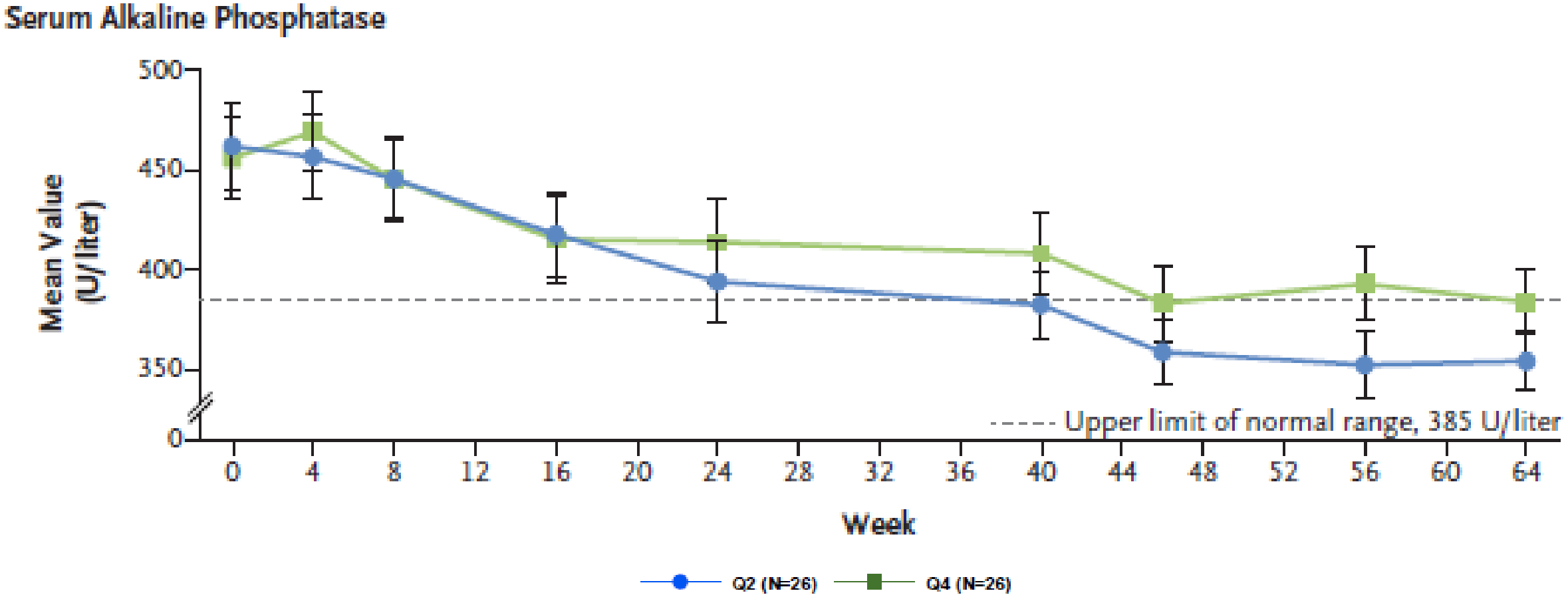
Reduced serum Alkaline Phosphatase



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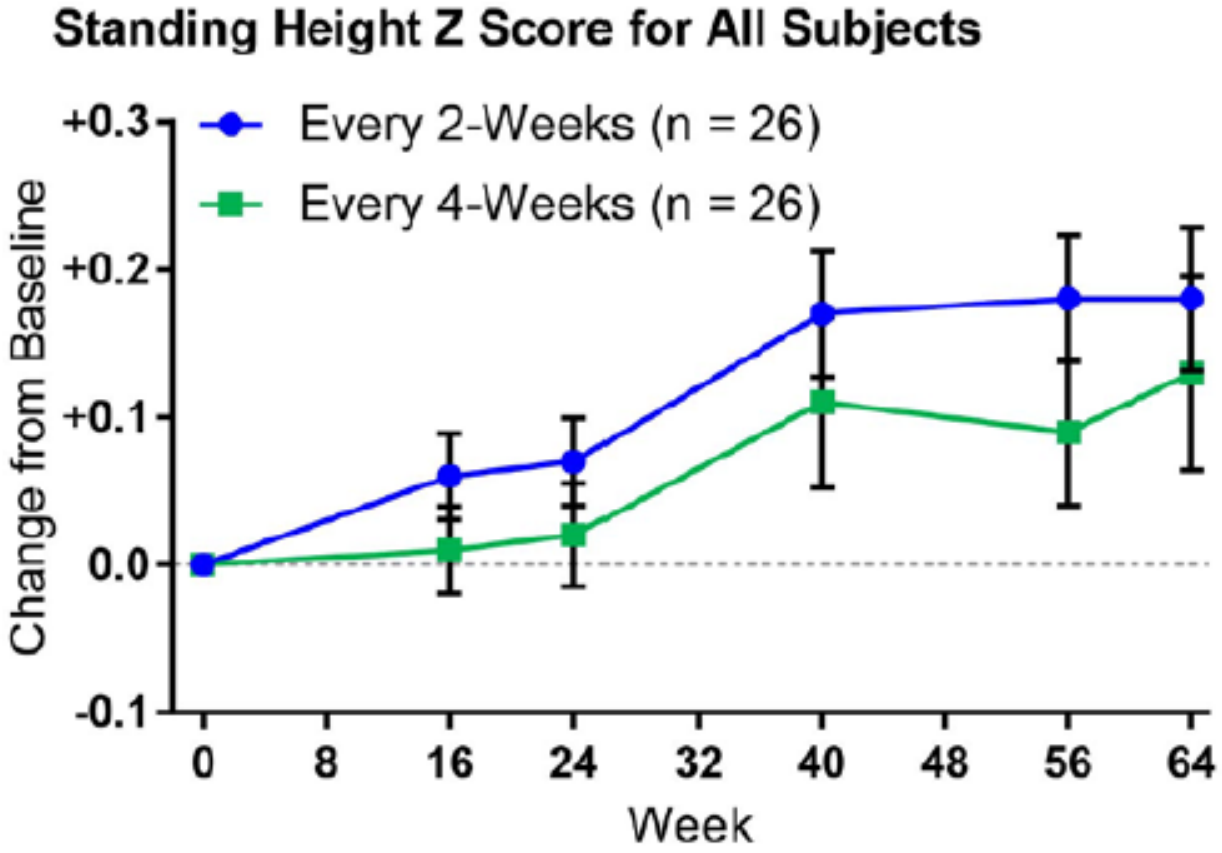
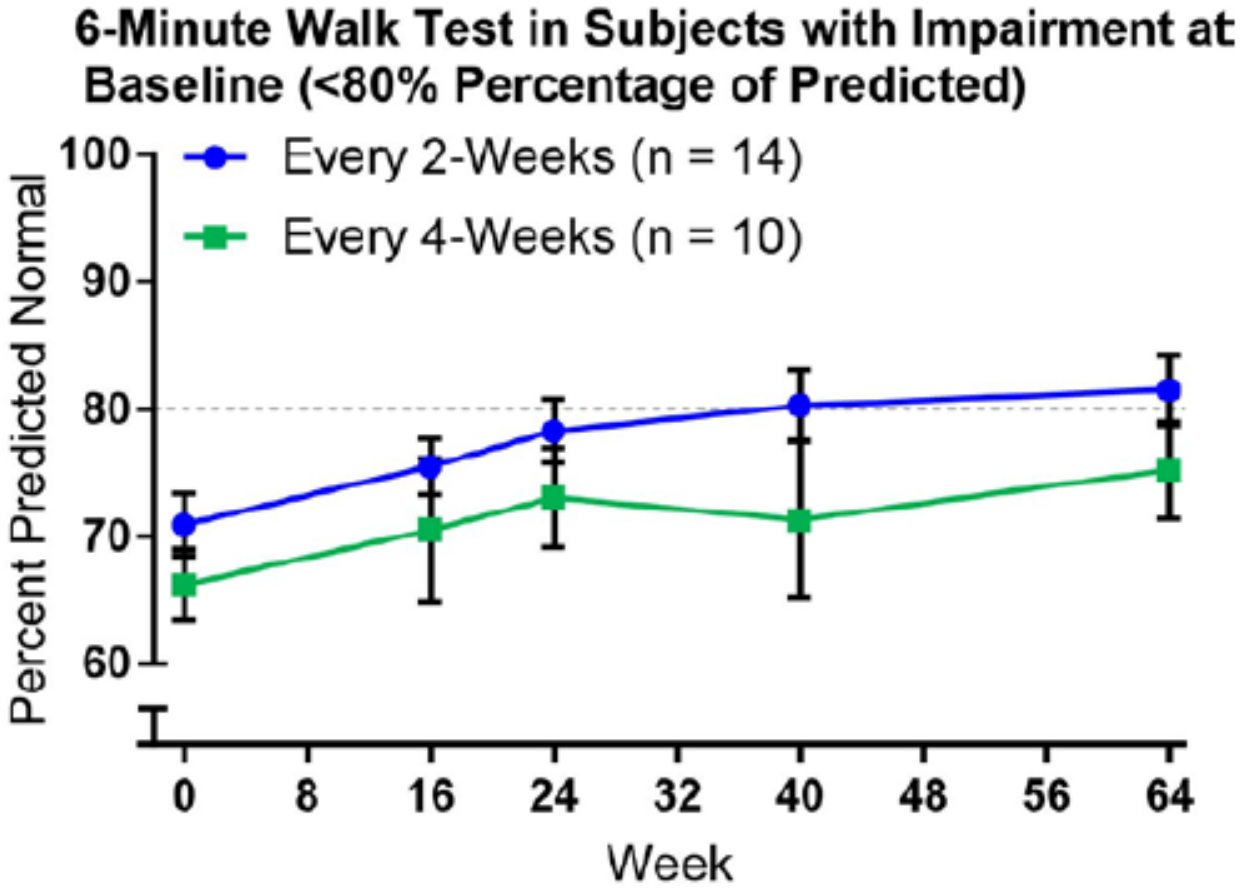
Effect on growth and walking





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Adverse events

Variable	Burosumab Every 2 Weeks (N = 26)	Burosumab Every 4 Weeks (N = 26)	All Patients (N = 52)
		no. of patients (%)	
Any adverse event	26 (100)	26 (100)	52 (100)
Adverse events with ≥15% incidence in both groups combined			
Injection-site reaction*	17 (65.4)	13 (50.0)	30 (57.7)
Headache	16 (61.5)	10 (38.5)	26 (50.0)
Cough	15 (57.7)	8 (30.8)	23 (44.2)
Nasopharyngitis	8 (30.8)	13 (50.0)	21 (40.4)
Pain in extremity	9 (34.6)	12 (46.2)	21 (40.4)
Upper respiratory tract infection	9 (34.6)	9 (34.6)	18 (34.6)
Vomiting	10 (38.5)	8 (30.8)	18 (34.6)
Arthralgia	7 (26.9)	10 (38.5)	17 (32.7)
Pyrexia	8 (30.8)	8 (30.8)	16 (30.8)
Rash	7 (26.9)	6 (23.1)	13 (25.0)
Seasonal allergy	5 (19.2)	8 (30.8)	13 (25.0)

Carpenter *et al. N Engl J Med* 2018;378:1987-98

Summary

- XLH is caused by mutations in PHEX
- Increased FGF23 activity results in rickets
- Burosumab is an effective treatment for XLH

Thank you – questions?