The many faces of FGF23

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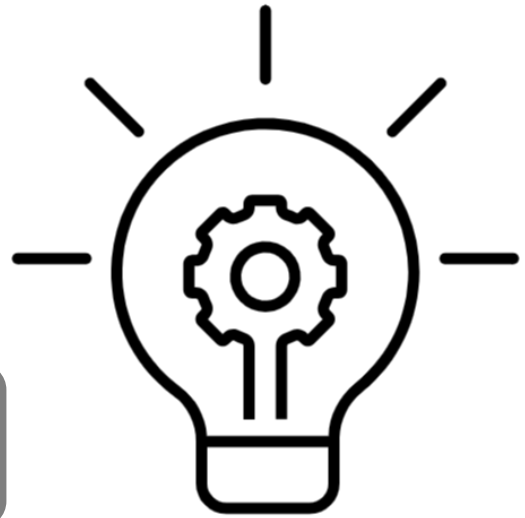
IES 2022

FGF23 discovery



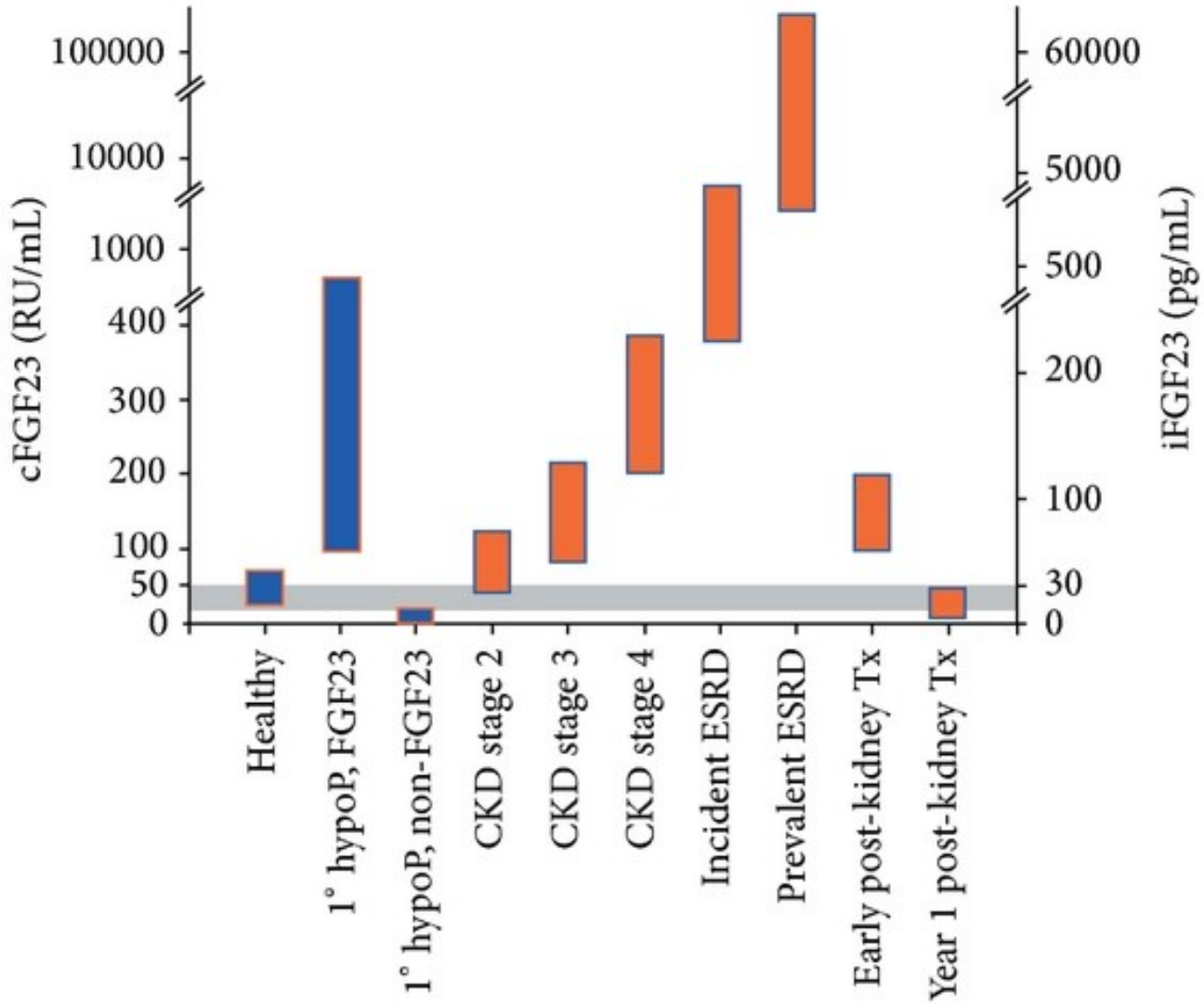
The first identification of Fibroblast growth factor 23 (FGF23) was through gene analyses in patients with AD or X-linked hypophosphatemic rickets

The discovery of FGF23 has revolutionized understanding of mineral metabolism

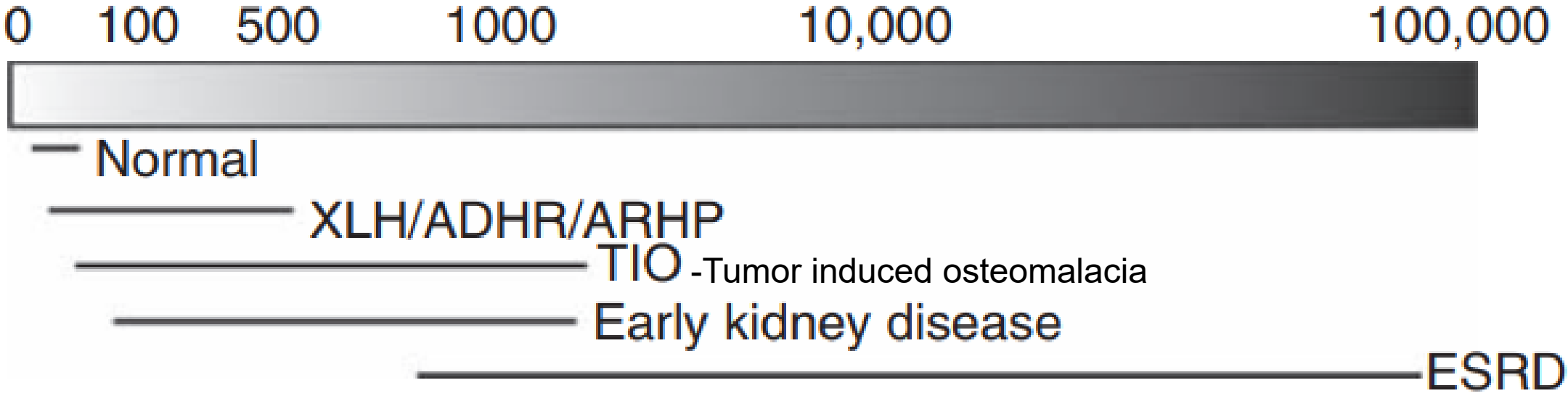
Data on the multiple effects of FGF23 have been collected

Kuro-O M, et al. FGF23-αKlotho as a paradigm for a kidney-bone network. Bone. 2017

The spectrum of FGF23 derived disease

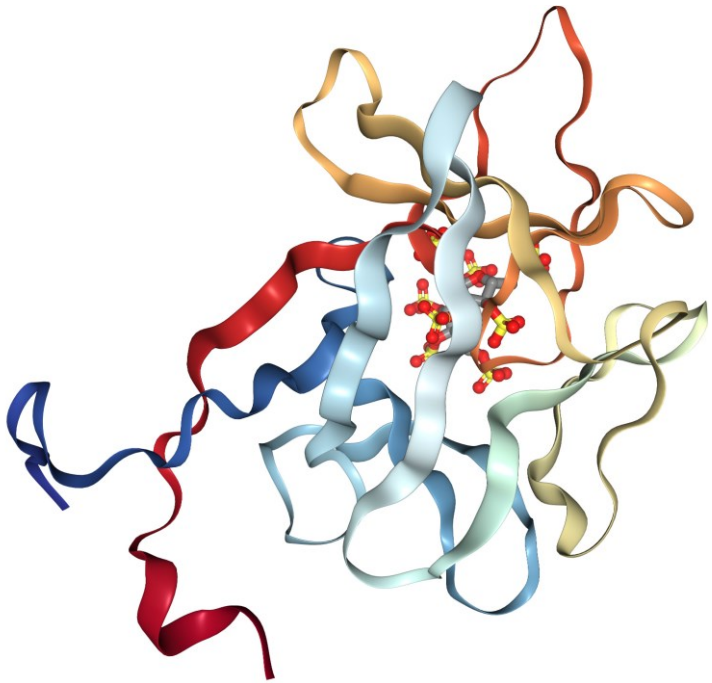


Schnedl C et al. FGF23 in Acute and Chronic Illness. Dis Markers. 2015



Jüppner H. Phosphate and FGF-23. Kidney Int Suppl. 2011

The spectrum of FGF23 derived disease

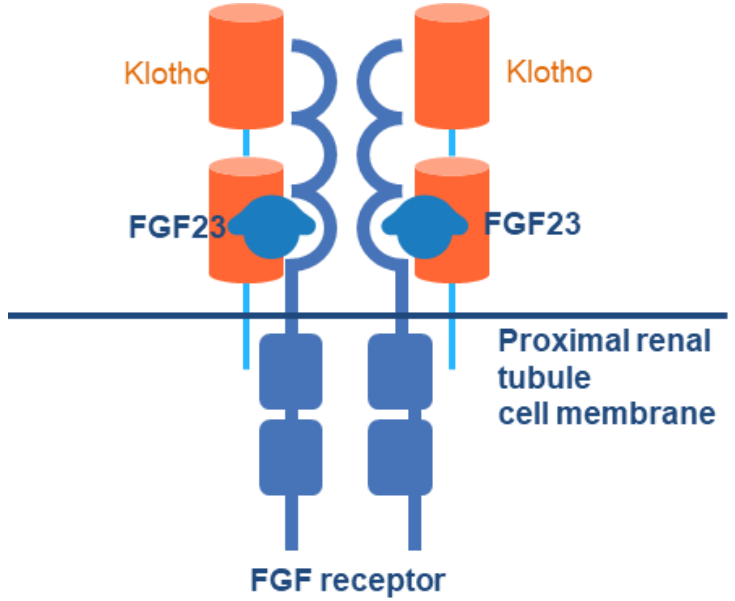


Fibroblast growth factor-23

A bone-derived hormone, secreted by osteocytes and osteoblasts

Physiologic actions on target tissues mediated by FGF receptors

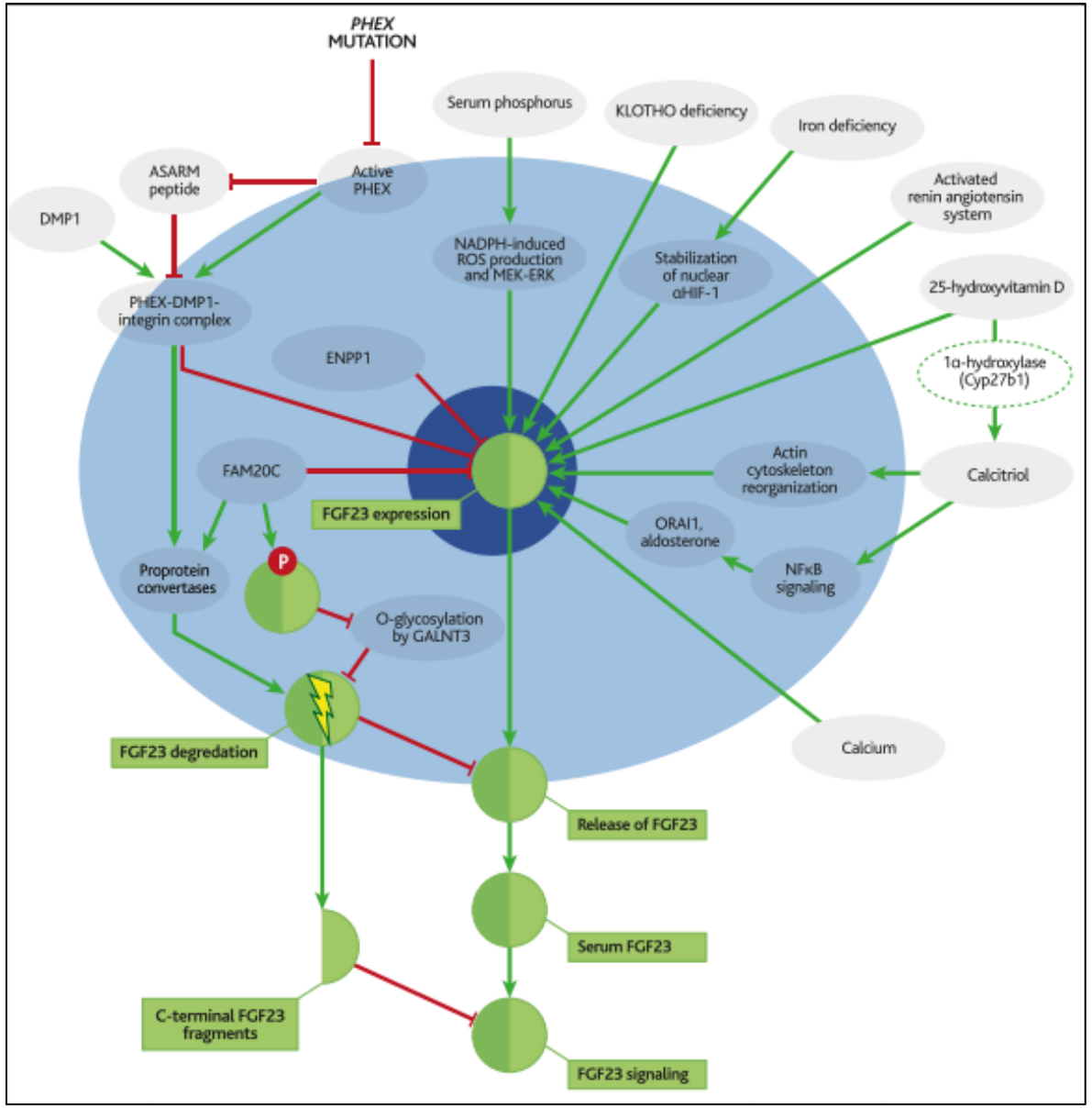
Klotho functions as a co-receptor, increases binding affinity



Activation of signalling pathway

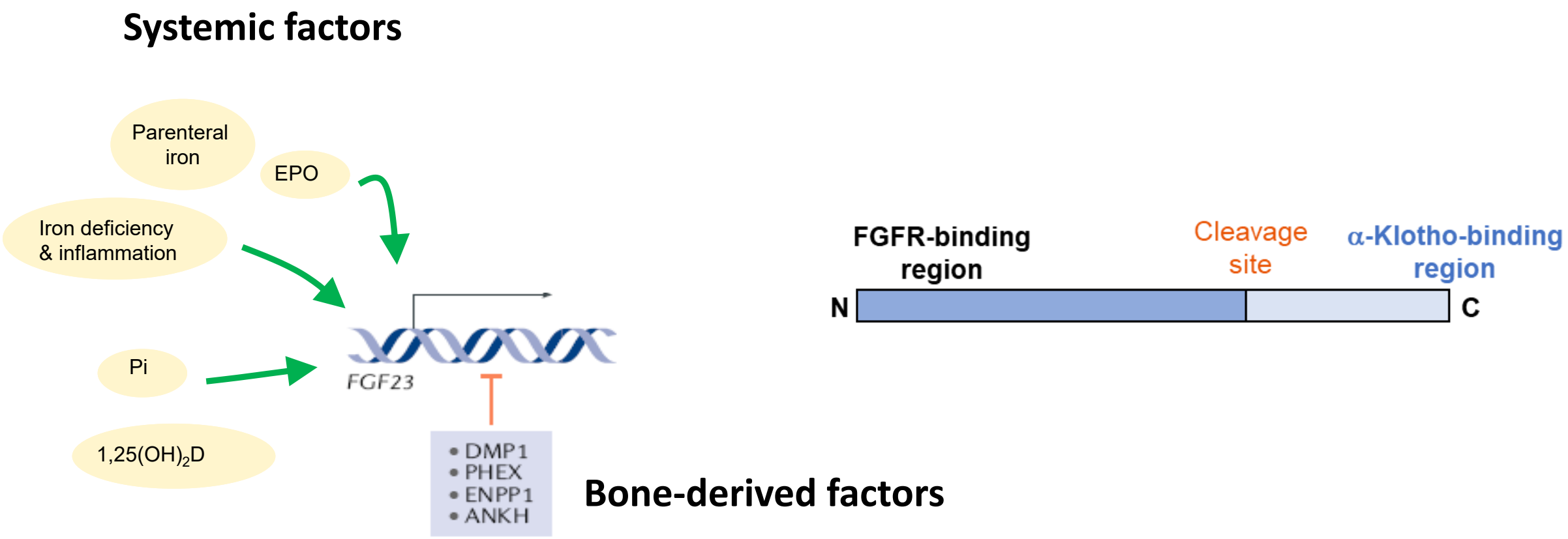
Liu S et al. How fibroblast growth factor 23 works. J Am Soc Nephrol. 2007
Beck-Nielsen S, et al. FGF23 and its role in X-linked hypophosphatemia-related morbidity Orphanet J Rare Dis. 2019

FGF23 regulation



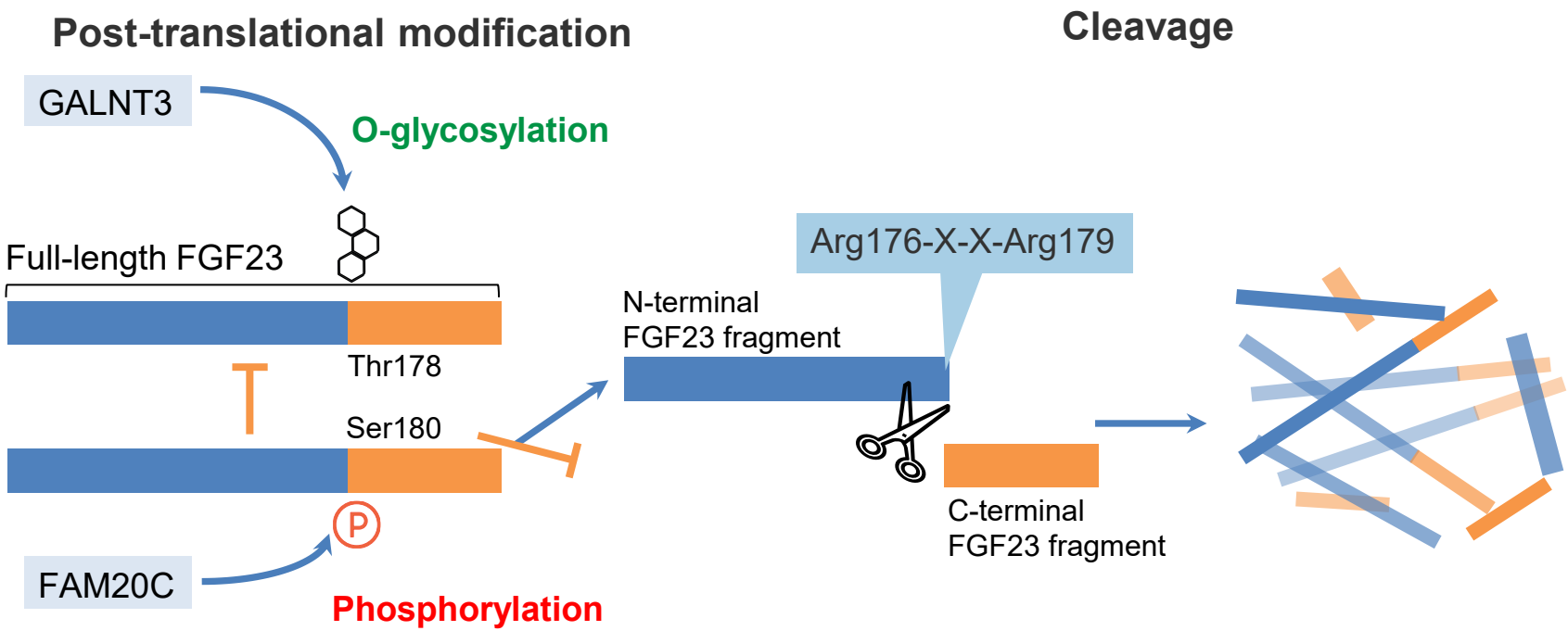
Beck-Nielsen SS, et al. FGF23 and its role in X-linked hypophosphatemia-related morbidity. Orphanet J Rare Dis. 2019

FGF23 transcription regulation



Bär L, et al. Regulation of fibroblast growth factor 23 (FGF23) in health and disease. FEBS Lett. 2019

Post-translational modification determines FGF23 processing



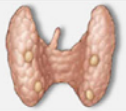
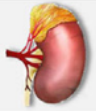
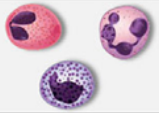
Following translation, intact FGF23 can be modified by glycosylation/phosphorylation

Glycosylated FGF23 is protected from proteolytic cleavage and is considered the biologically active form

Phosphorylated FGF23 is cleaved, generating N- and C-terminal fragments

Edmonston D, et al. FGF23 at the crossroads of phosphate, iron economy and erythropoiesis. Nat Rev Nephrol. 2020

Multiple target organs

							
Cell type	Parathyroid chief cells	Renal tubular epithelial cells	Renal fibroblasts	Cardiac myocytes	Cardiac fibroblasts	Hepatocytes	Macrophages	Neutrophils
Klotho	+	+	-	-	-	-	?	-
FGFR isoform	1	1	4	4	?	4	1	2
Signal mediators	FRS2α/Ras/ MAPK	FRS2α/Ras/ MAPK	PLCγ/calcineurin/ NFAT	PLCγ/calcineurin/ NFAT	?	PLCγ/calcineurin/ NFAT	FRS2α/Ras/ MAPK	PKA/Rap1
Cellular effects	Decreased PTH expression	• Downregulation of NaPi-2a/c transporters • Inhibition of CYP27B1 • Activation of CYP24A1	• Increased TGFβ production • Activation	Hypertrophic growth	• Activation • Proliferation	Increased IL-6 and CRP expression	Increased TNFα production	• Decreased integrin activation • Increased rolling velocity
Organ effects	Suppression of PTH secretion	• Reduction of phosphate uptake • Reduction of vitamin D activation	Fibrosis	Hypertrophy	Fibrosis	Elevation of IL-6 and CRP secretion	-	-
Systemic effects	Reduced serum levels of PTH and calcium	Reduced serum levels of phosphate and 1,25D	Kidney failure	• Heart failure • Compensatory remodeling	Heart failure	Inflammation	Impaired immune response	• Reduced leukocyte recruitment • Impaired host defense

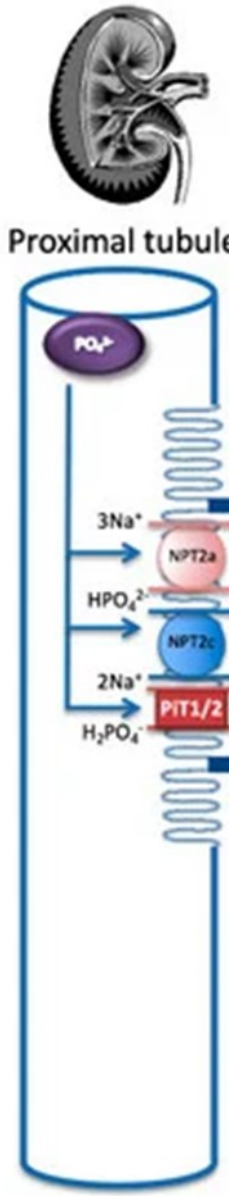
Richter B et al. FGF23 Actions on Target Tissues-With and Without Klotho. Front Endocrinol 2018

Direct target organ: the kidney

Phosphaturic effect:

Downregulating of the sodium-dependent phosphate transporters (NaPi-2a and NaPi-2c) in the proximal tubule

Increased urinary phosphate excretion

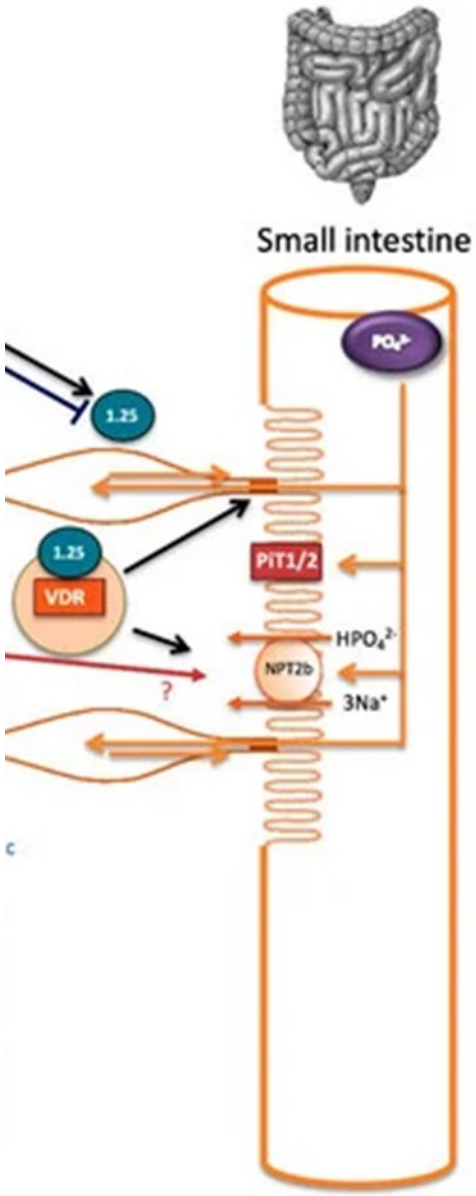


Indirect target organ: GIT

Vitamin D suppression:

- Inhibition of 1-α-hydroxylase (CYP27B1)- 25-hydroxyvitamin D→1,25-dihydroxyvitamin
- Stimulation of 24-hydroxylase (CYP24A1)- degrades 1,25D into inactive metabolites

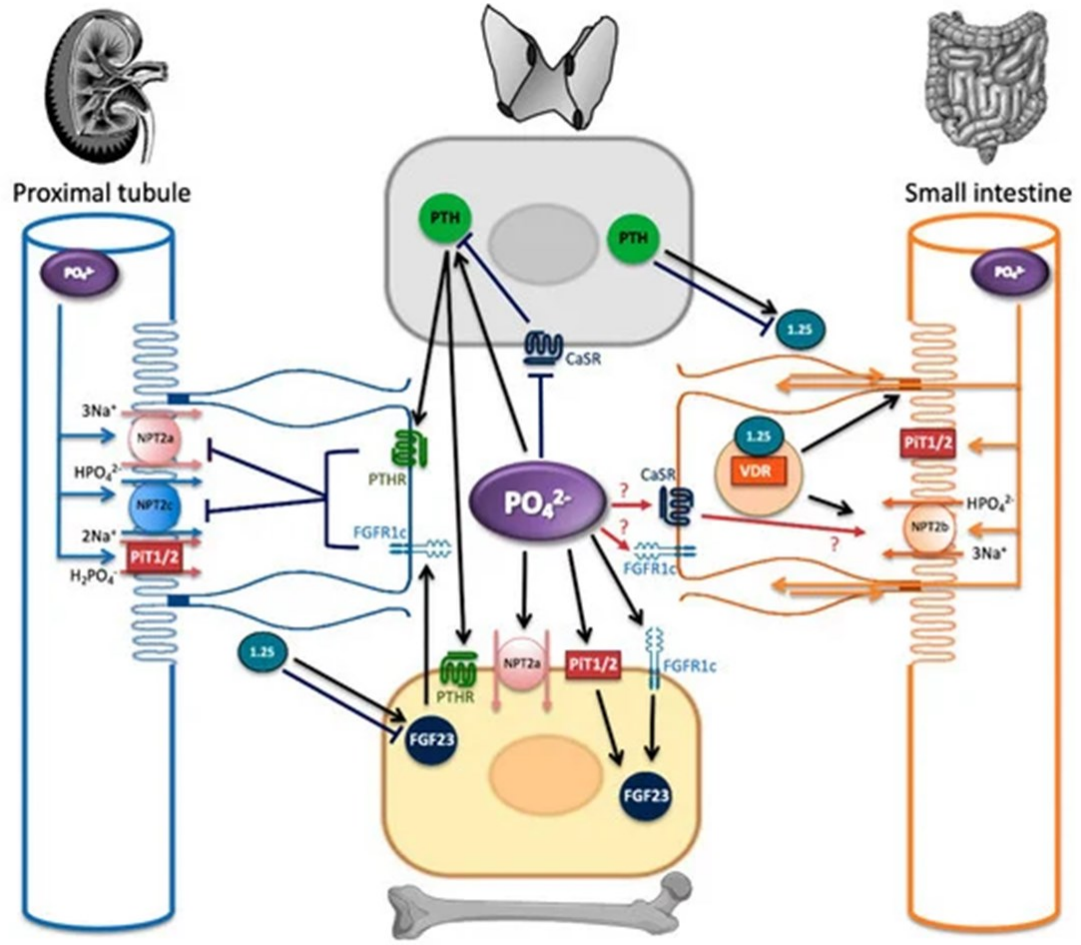
Decreased intestinal phosphate reabsorption



Target organ: parathyroid glands

Inhibition of PTH secretion

Further contribution to FGF23 phosphaturic and VitD suppressive effects



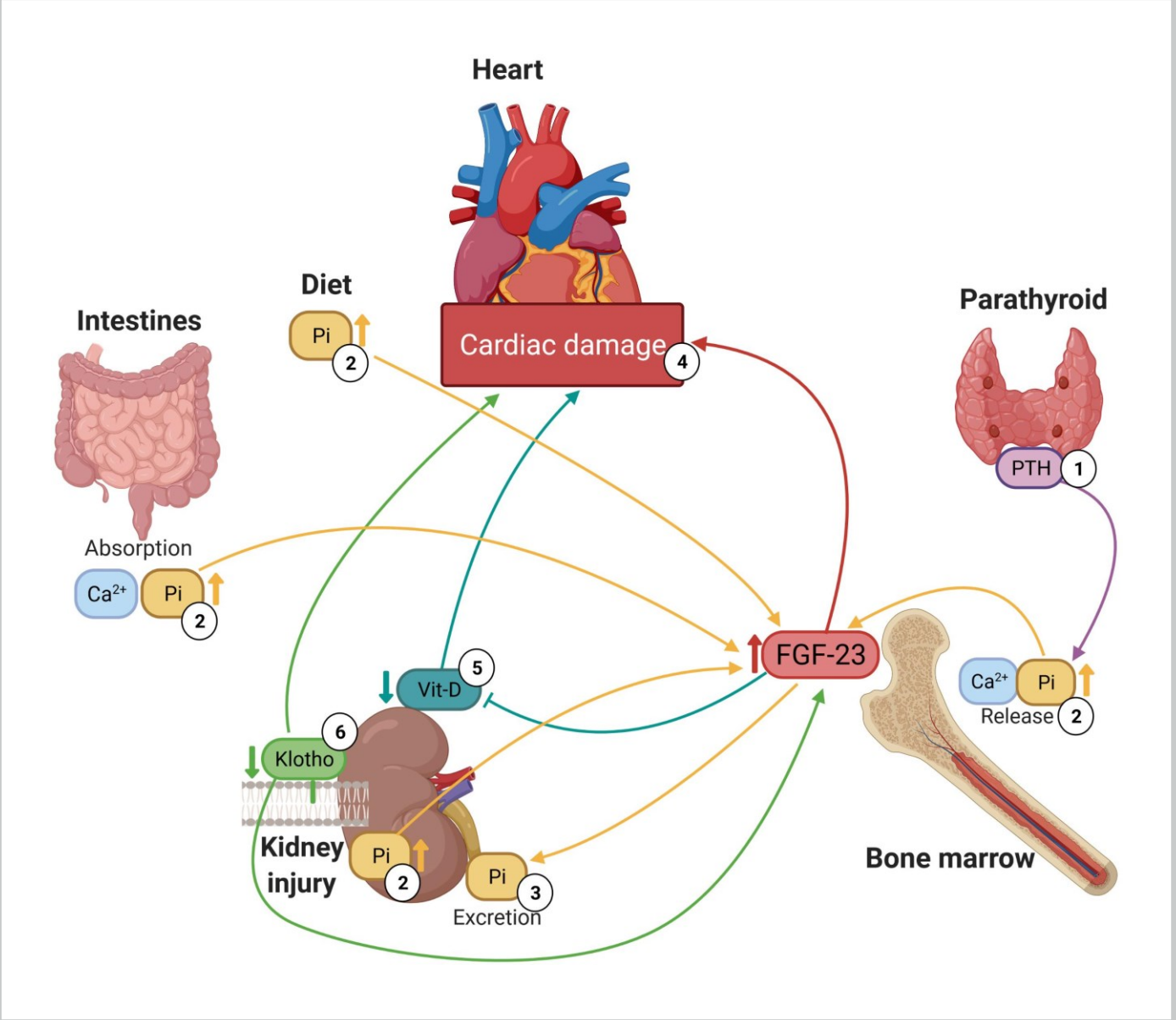
L Figueres et al. The Complexities of Organ Crosstalk in Phosphate Homeostasis: Time to Put Phosphate Sensing Back in the Limelight. Int J Mol Science 2021

Target organ: the heart

Recent evidence: high plasma FGF23 is a hallmark of cardiac damage

In chronic kidney disease:

- Serum phosphate levels increase and stimulate FGF-23
- FGF23 contributes to adverse cardiovascular events like LVH and heart failure



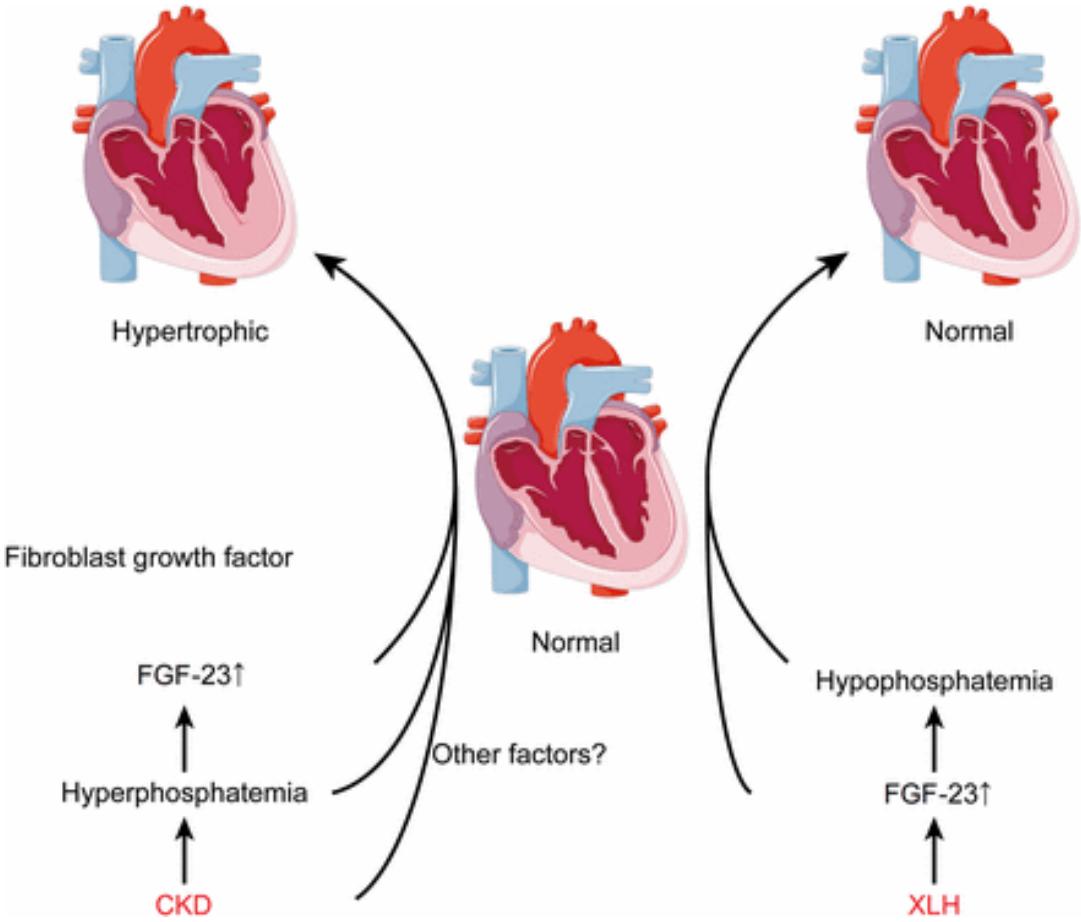
Vázquez-Sánchez S, et al. An Overview of FGF-23 as a Novel Candidate Biomarker of Cardiovascular Risk. Front Physiol. 2021

Target organ: the heart

The role of FGF-23 in cardiac disturbances is not clear

According to *In vivo* and *in vitro* studies FGF23 induces:

- cardiac remodeling and hypertrophy
- endothelial damage
- accelerated atherosclerosis



Bao JF, et al. A Land of Controversy: Fibroblast Growth Factor-23 and Uremic Cardiac Hypertrophy. J Am Soc Nephrol. 2020

XLH- X linked hypophosphatemia

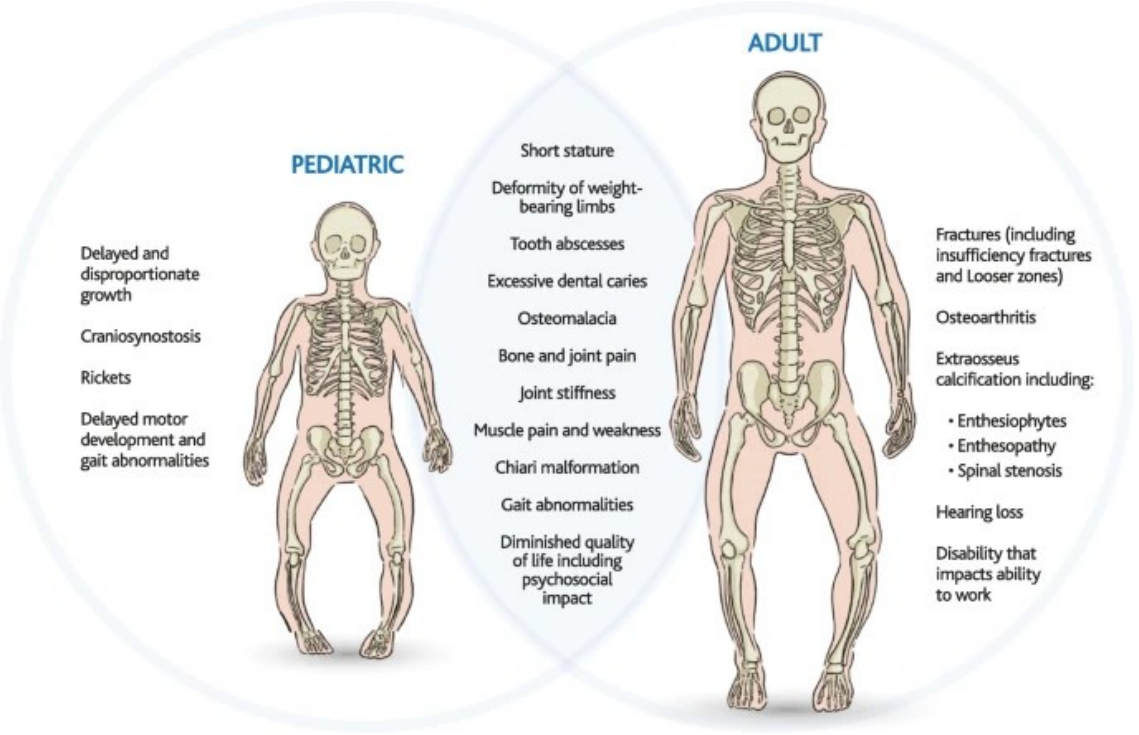
The most common form of heritable rickets: phosphate-regulating endopeptidase homolog X-linked (*PHEX*) gene mutation

Increased FGF23 causes:

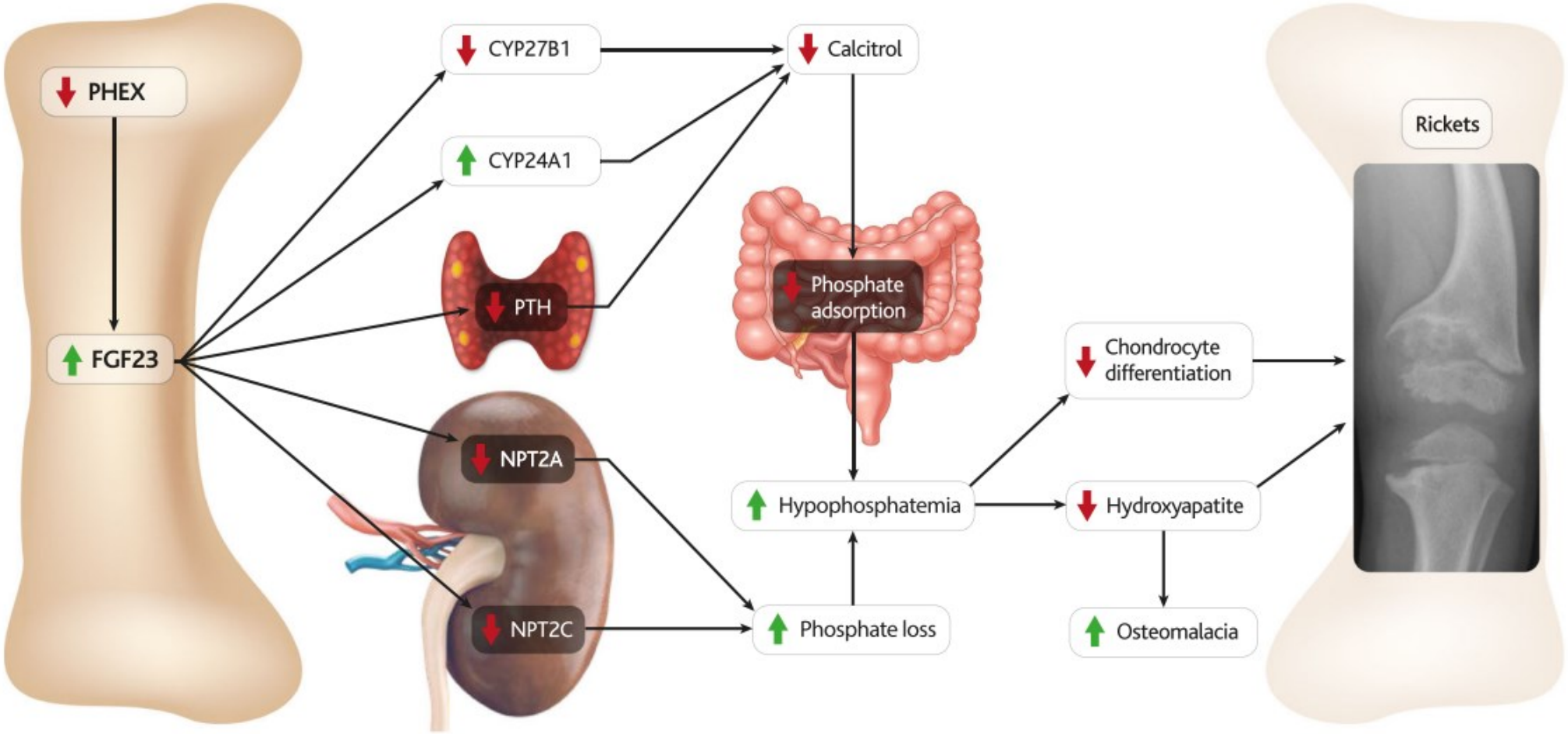
Phosphaturia

↓ Phosphate

↓ 1,25(OH)$_2$D3



Beck-Nielsen SS, et al. FGF23 and its role in X-linked hypophosphatemia-related morbidity. Orphanet J Rare Dis. 2019

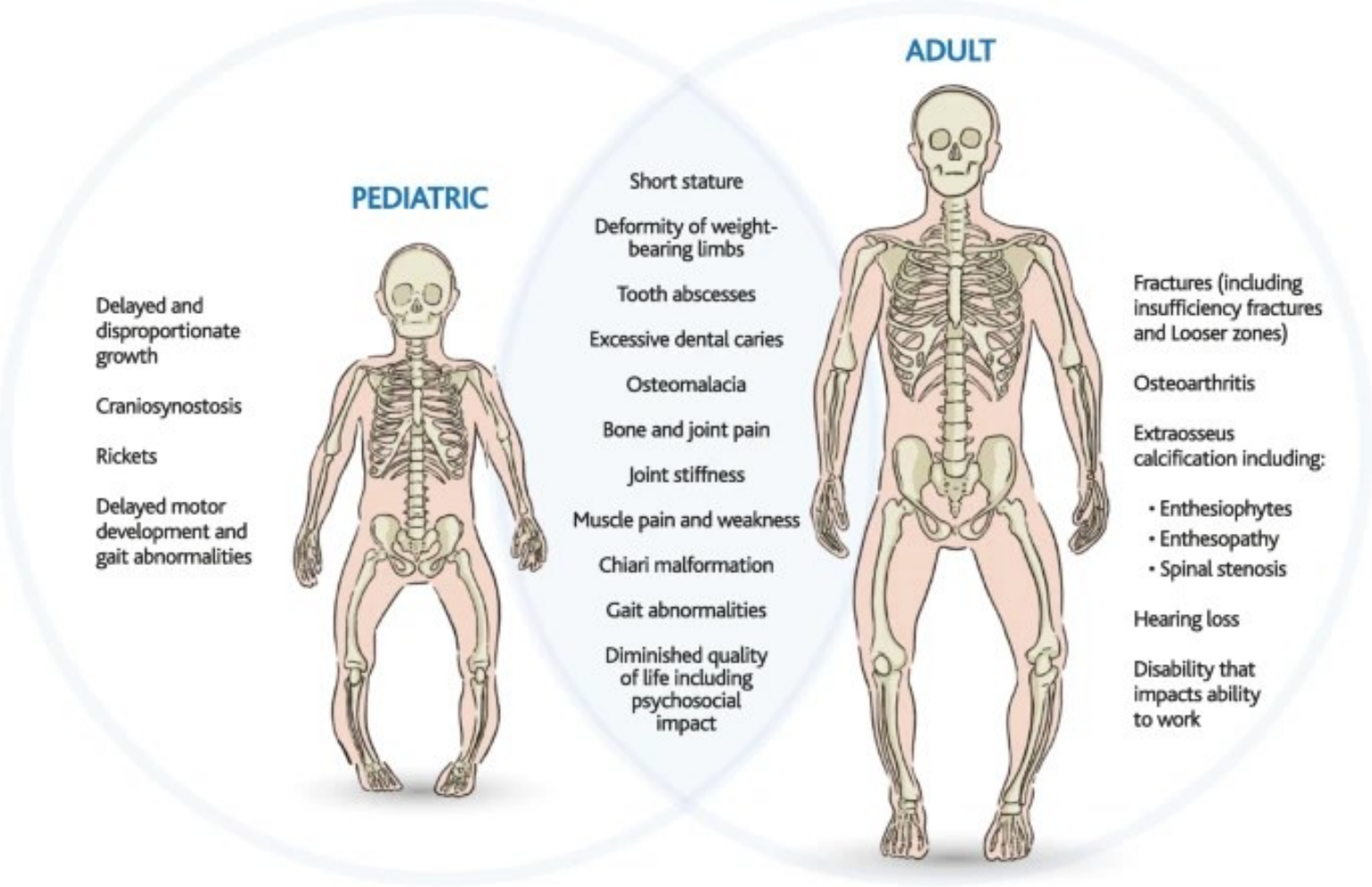


Beck-Nielsen SS, et al. FGF23 and its role in X-linked hypophosphatemia-related morbidity. Orphanet J Rare Dis. 2019

XLH- x linked hypophosphatemia

Clinical manifestations:

- Short stature
- Limb deformities
- Frontal bossing
- Dental abscesses



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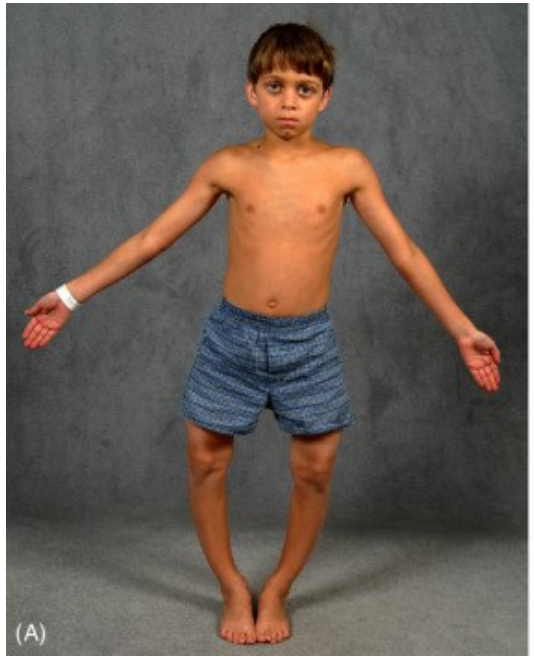

(A)


(B)


(C)


IES 2022

XLH- treatment

Conventional treatment:

Multiple daily doses of Calciless + αD3

Difficult to maintain

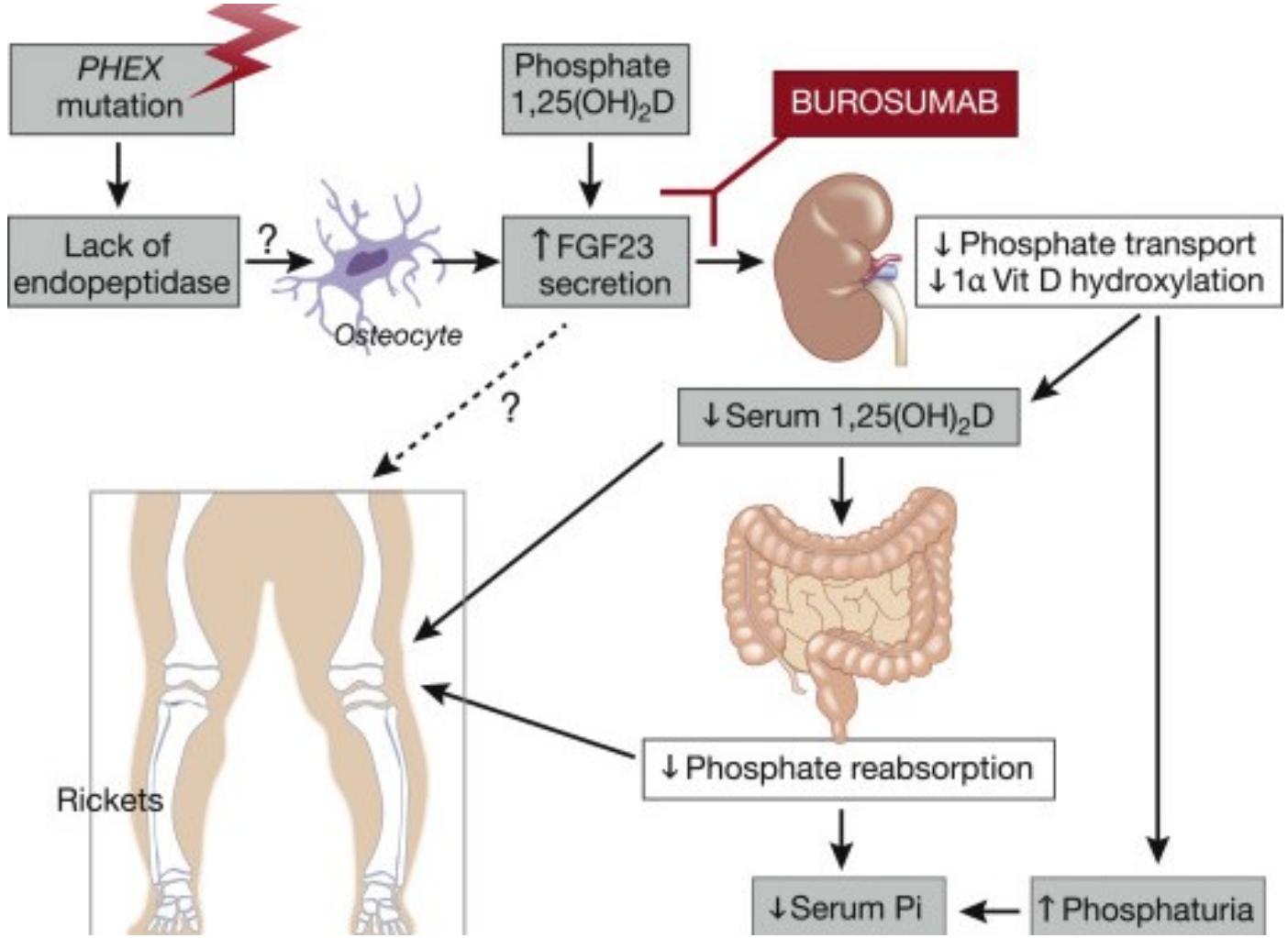
Persistence of rickets

XLH-treatment

New treatment:

Burosumab (Crysvita)-
anti-FGF23 immunoglobulin

Administered SC every 2 weeks



Emma F, Haffner D. FGF23 blockade coming to clinical practice. Kidney Int. 2018

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Burosumab Therapy in Children with X-Linked Hypophosphatemia

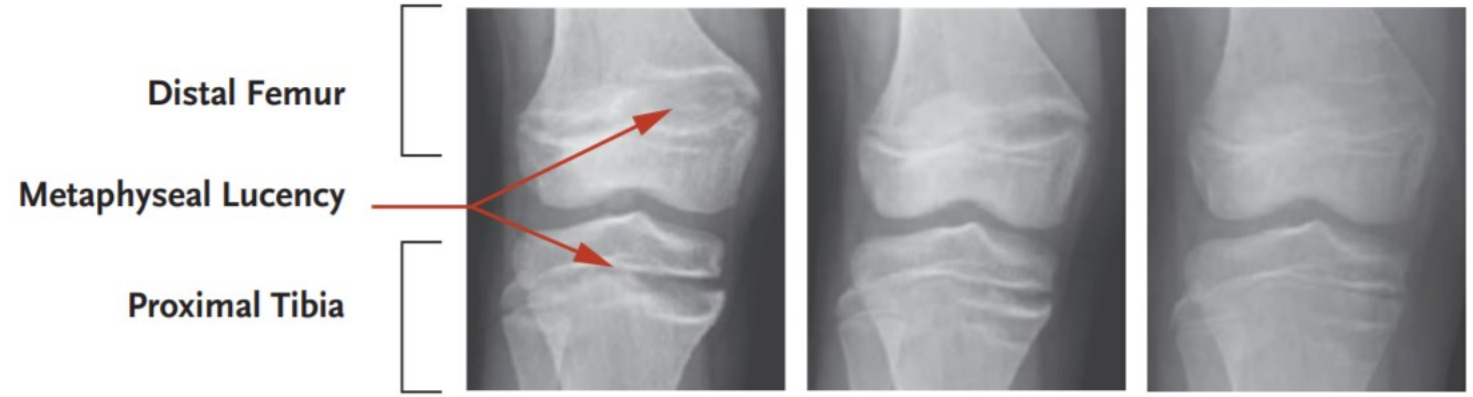
Thomas O. Carpenter, M.D., Michael P. Whyte, M.D., Erik A. Imel, M.D.,

Since 2018 - burosumab, a novel treatment for XLH has been introduced

Improved biochemical markers (↓urine phosphate, ↑serum phosphate, ↓alk phos)

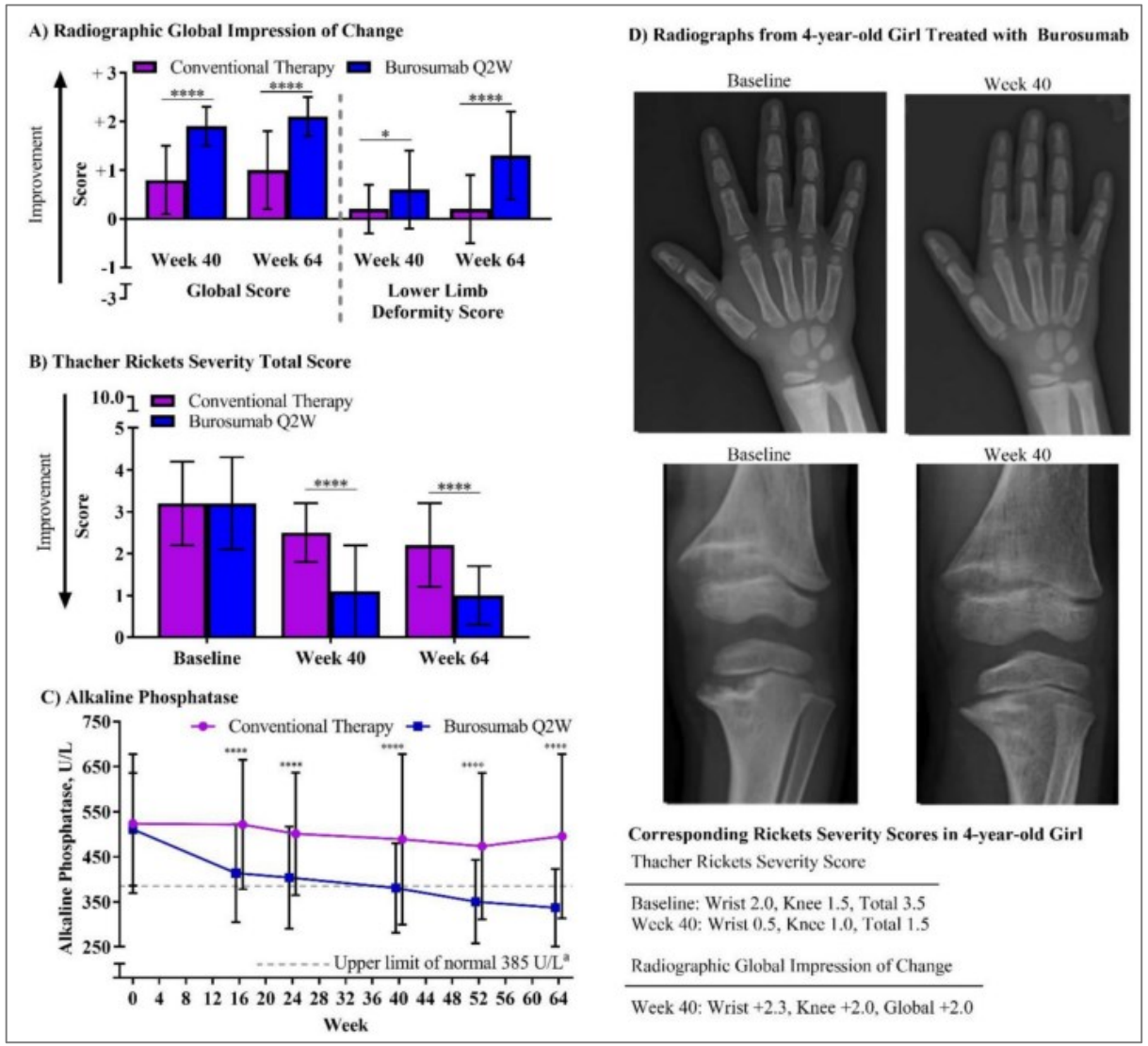
- Burosumab heals rickets
- Reduces limb pain, improves physical activity capability
- Improves linear growth

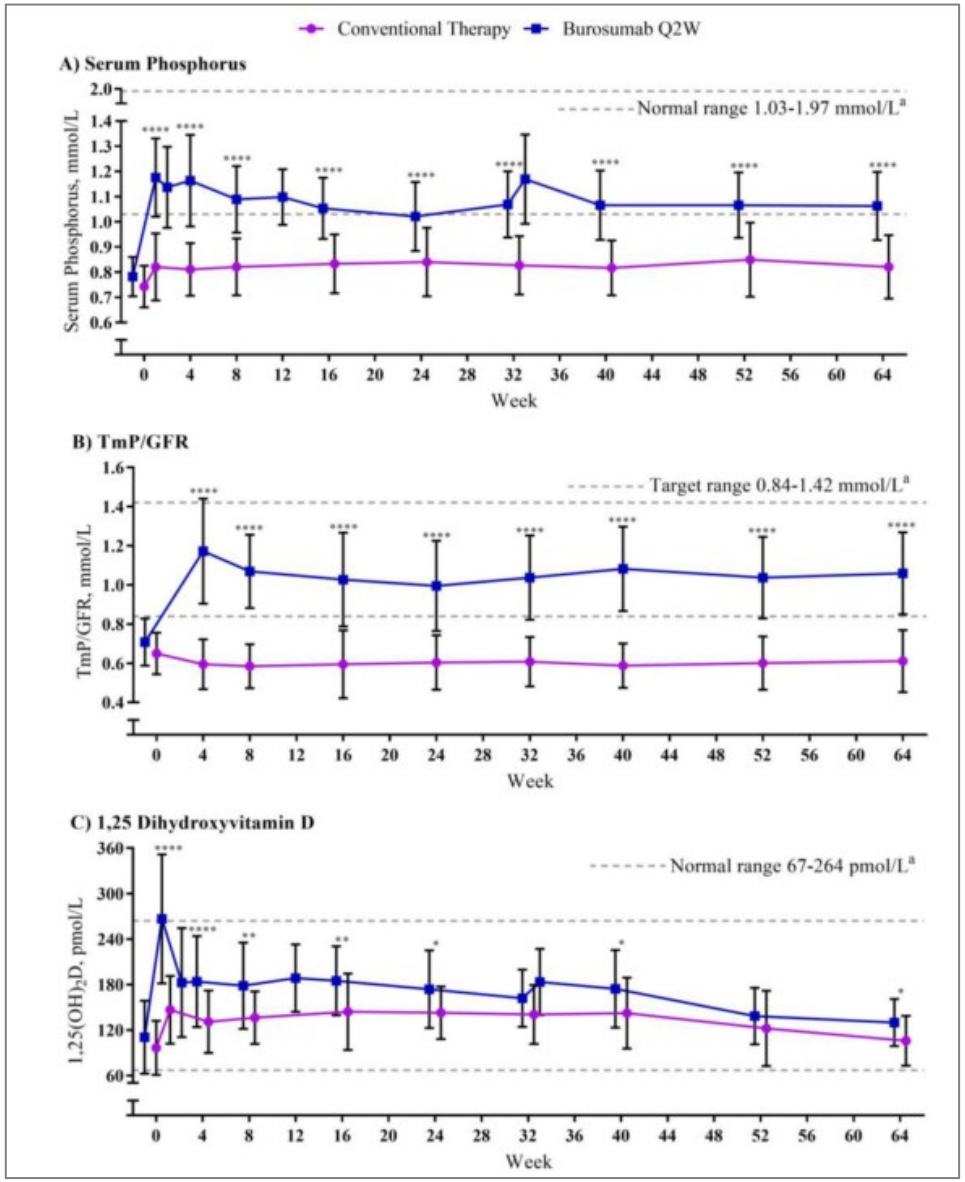
C Radiographs of the Knee in an 11-Year-Old Girl



	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

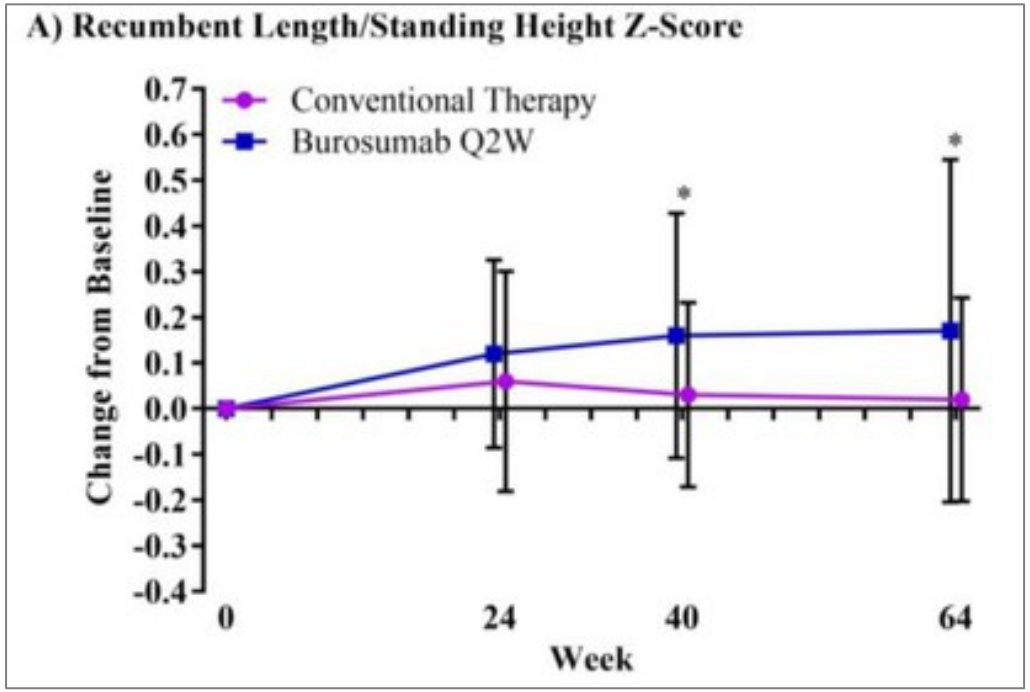
Carpenter TO, et al. Burosumab Therapy in Children with X-Linked Hypophosphatemia. N Engl J Med. 2018



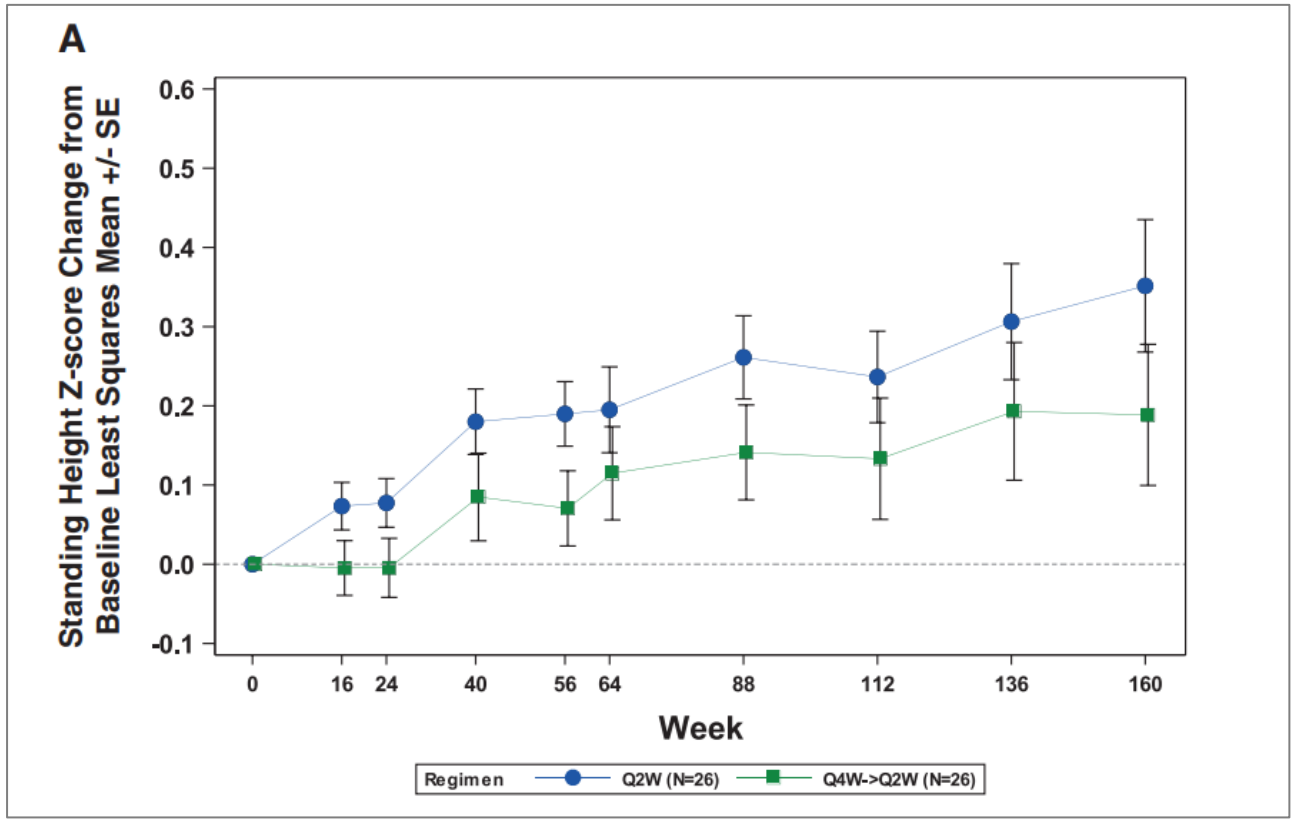


Imel EA, et al. Burosumab versus conventional therapy in children with X-linked hypophosphataemia: a randomised, active-controlled, open-label, phase 3 trial. Lancet. 2019

Burosumab therapy improves linear growth



Imel EA, et al. Burosumab versus conventional therapy in children with X-linked hypophosphataemia: a randomised, active-controlled, open-label, phase 3 trial. Lancet. 2019



Linglart A, et al. Sustained Efficacy and Safety of Burosumab, a Monoclonal Antibody to FGF23, in Children With X-Linked Hypophosphatemia. J Clin Endocrinol Metab. 2022

2021

Body composition and cardiometabolic health of pediatric patients with X-linked hypophosphatemia (XLH) under burosumab therapy

Avivit Brener, Yael Lebenthal, Roxana Cleper, Livia Kapusta and Leonid Zeitlin

Increased prevalence of obesity in pediatric XLH

- 1/3 of our XLH patients were overweight/obese
- 71.4% had body fat% above the normal range
- The improvement observed in the ASMM percentile may be attributed to the improvement in patients' medical condition

Table 2. Twelve-month surveillance of 7 burosumab-treated XLH patients.

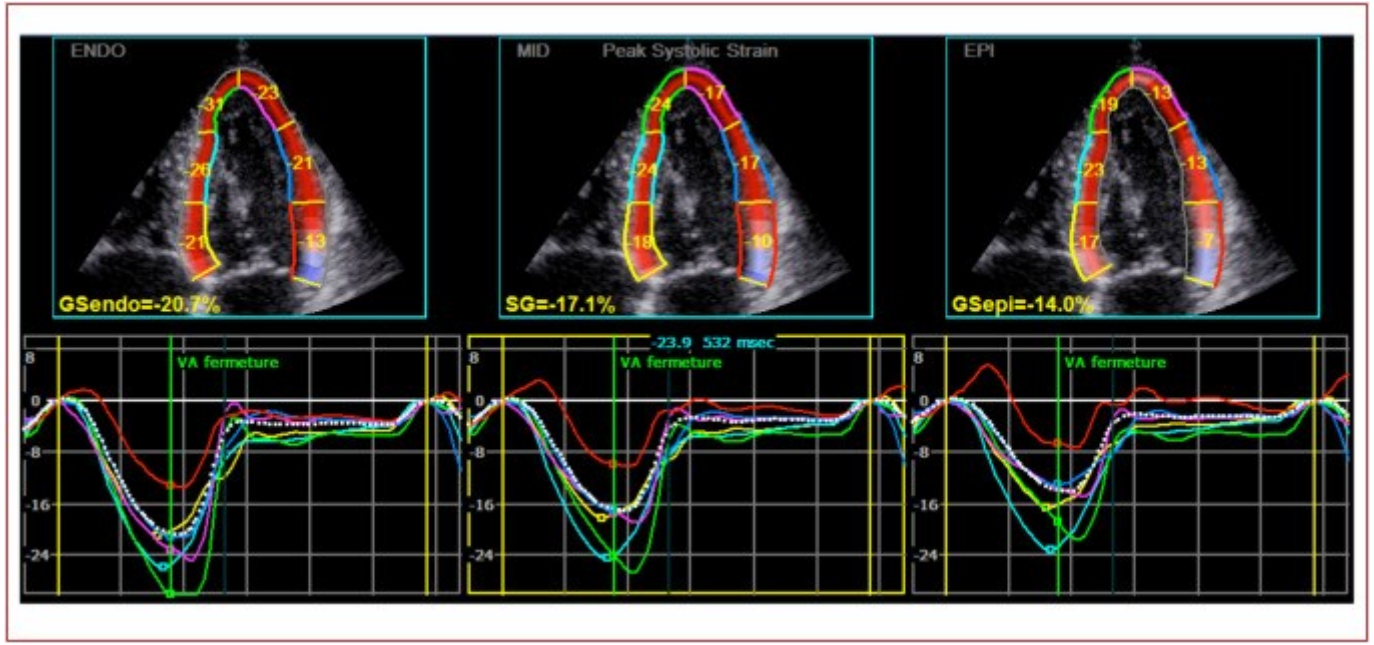
	Baseline	6 months	12 months	p^a	p^b
Body composition analysis					
Fat mass, kg	7.0 ± 3.1	7.2 ± 2.9	7.9 ± 4.1	0.313	0.231
Fat mass, %	24.40 ± 3.13	24.06 ± 2.18	24.24 ± 3.96	0.645	0.822
Fat-free mass, kg	21.1 ± 6.7	22.5 ± 6.9	23.5 ± 7.2	**0.001**	**0.046**
Fat-free mass, %	74.26 ± 2.93	75.82 ± 2.57	75.20 ± 3.65	0.175	0.497
Fat-free mass percentile	11.00 ± 9.98	18.86 ± 15.96	21.71 ± 14.82	0.068	0.518
ASMM, kg	7.4 ± 3.0	8.0 ± 3.2	8.4 ± 3.3	**0.012**	**0.034**
ASMM, %	25.28 ± 3.09	26.18 ± 3.01	26.32 ± 2.22	0.130	0.722
ASMM percentile	8.14 ± 8.45	22.00 ± 16.43	25.57 ± 19.60	**0.006**	0.356
Muscle-to-fat ratio (range)	1.06 ± 0.20 (0.87–1.56)	1.10 ± 0.15 (0.88–1.54)	1.11 ± 0.18 (0.78–1.63)	0.420	0.824

Zhukouskaya VV, et al. Increased prevalence of overweight and obesity in children with X-linked hypophosphatemia. Endocr Connect 2020
McCarthy HD. Body fat measurements in children as predictors for the metabolic syndrome: focus on waist circumference. Proc Nutr Soc. 2006

Burosumab and cardiac function

Aim: to detect early cardiac function alterations related to excess FGF23

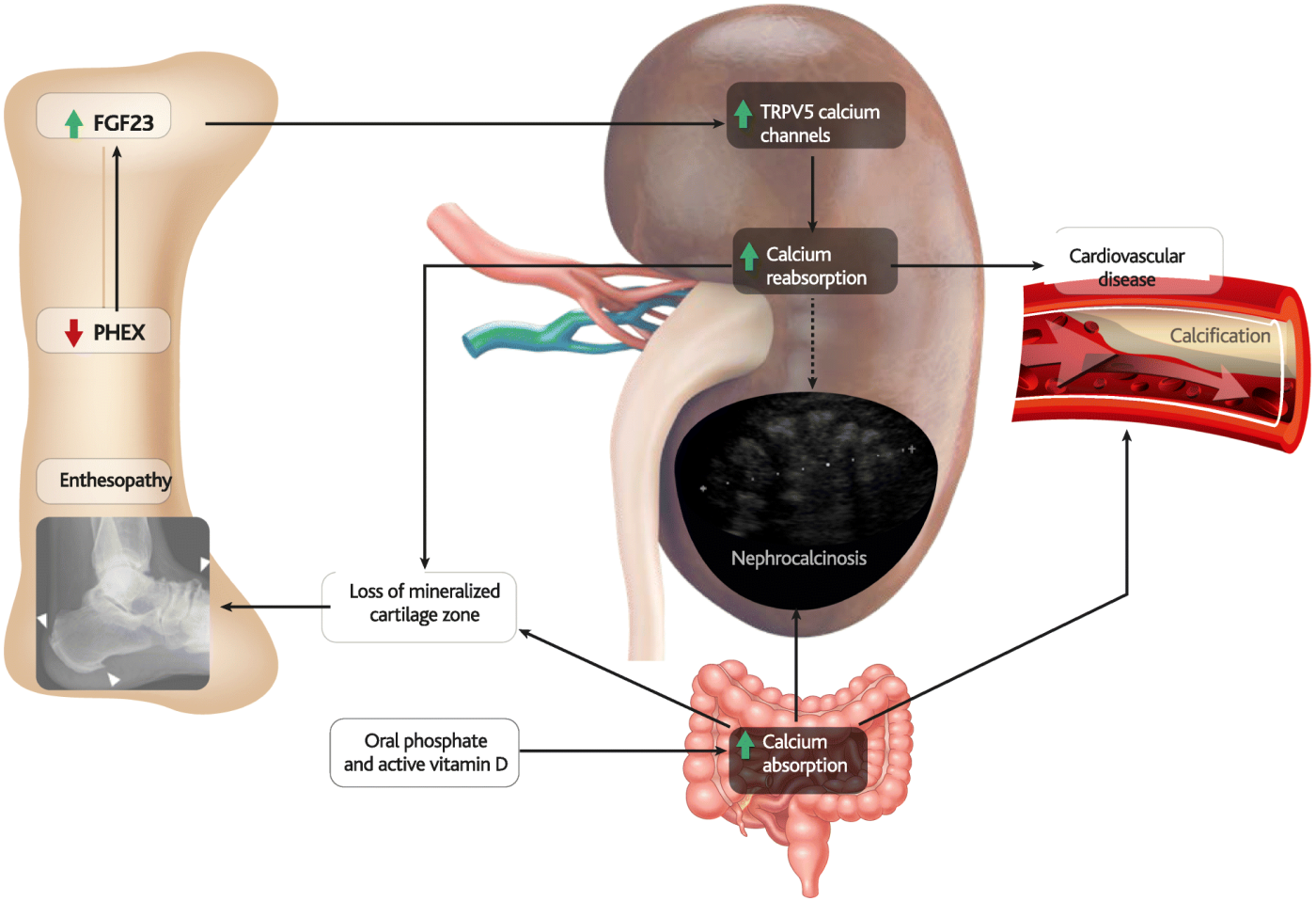
Methods: longitudinal follow up of **strain cardiac imaging** at burosumab initiation and once a year thereafter



Ancedy Y, et al. Does layer-specific strain using speckle tracking echocardiography improve the assessment of left ventricular myocardial deformation? A review. Arch Cardiovasc Dis. 2020

The heart is a 3D organ with a complex fiber arrangement. The strain measures systolic deformation that occurs after the application of stress

Burosumab and the kidney

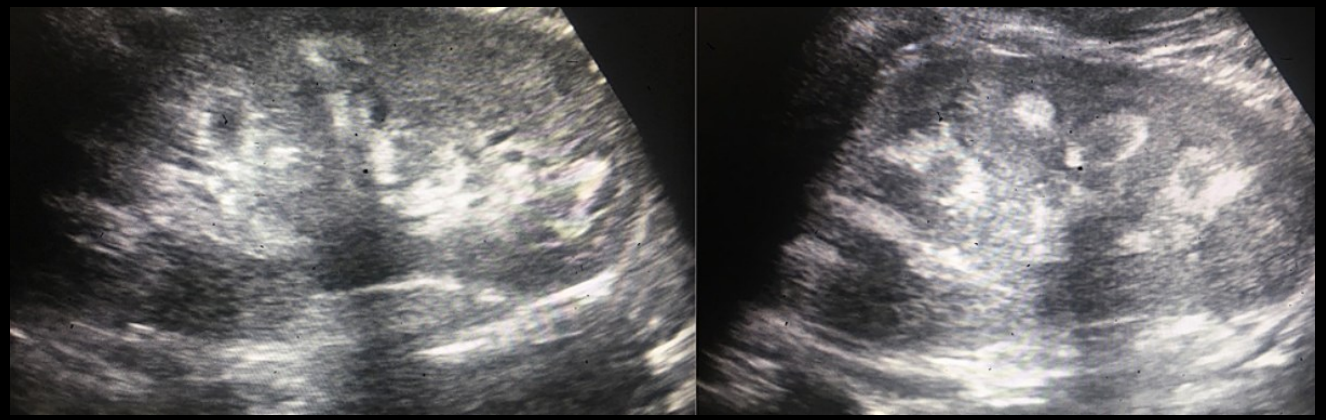


Beck-Nielsen SS, et al. FGF23 and its role in X-linked hypophosphatemia-related morbidity. Orphanet J Rare Dis. 2019

Burosumab and the kidney

Conventional treatment (phosphorus repletion and calcitriol) do not correct the underlying pathophysiological mechanism

Long term complication: nephrocalcinosis, HTN, CKD



Baradhi K. Dramatic Transformation After Burosumab in a Young Boy With X-linked Hypophosphatemia: A Life-Changing Saga. Cureus. 2022

Burosumab and the kidney

Aim: to characterize kidney structure and function throughout burosumab treatment

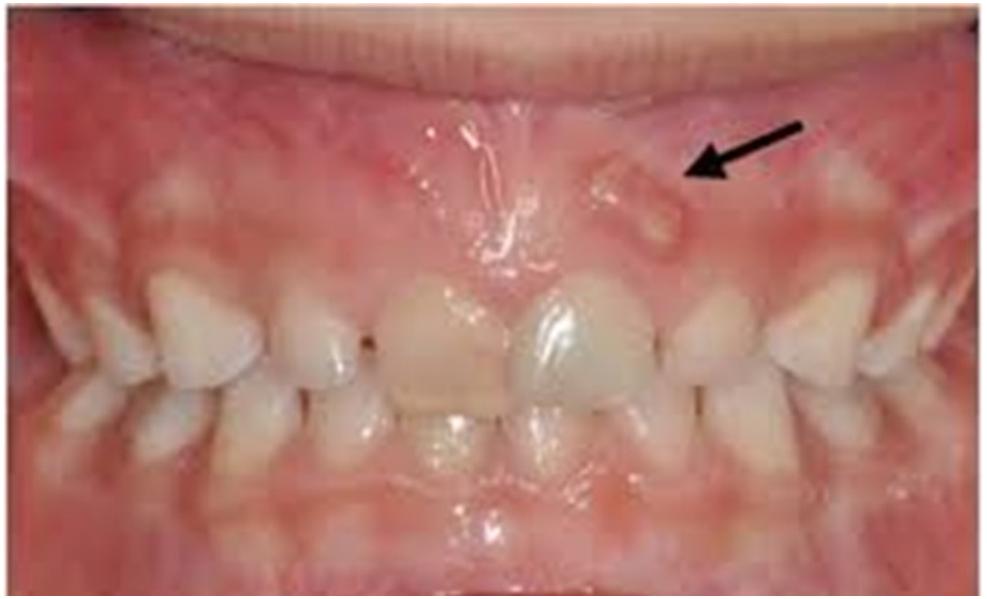
Methods: a multicenter study

Data collection: anthropometric measurements, blood pressure, laboratory evaluation, US

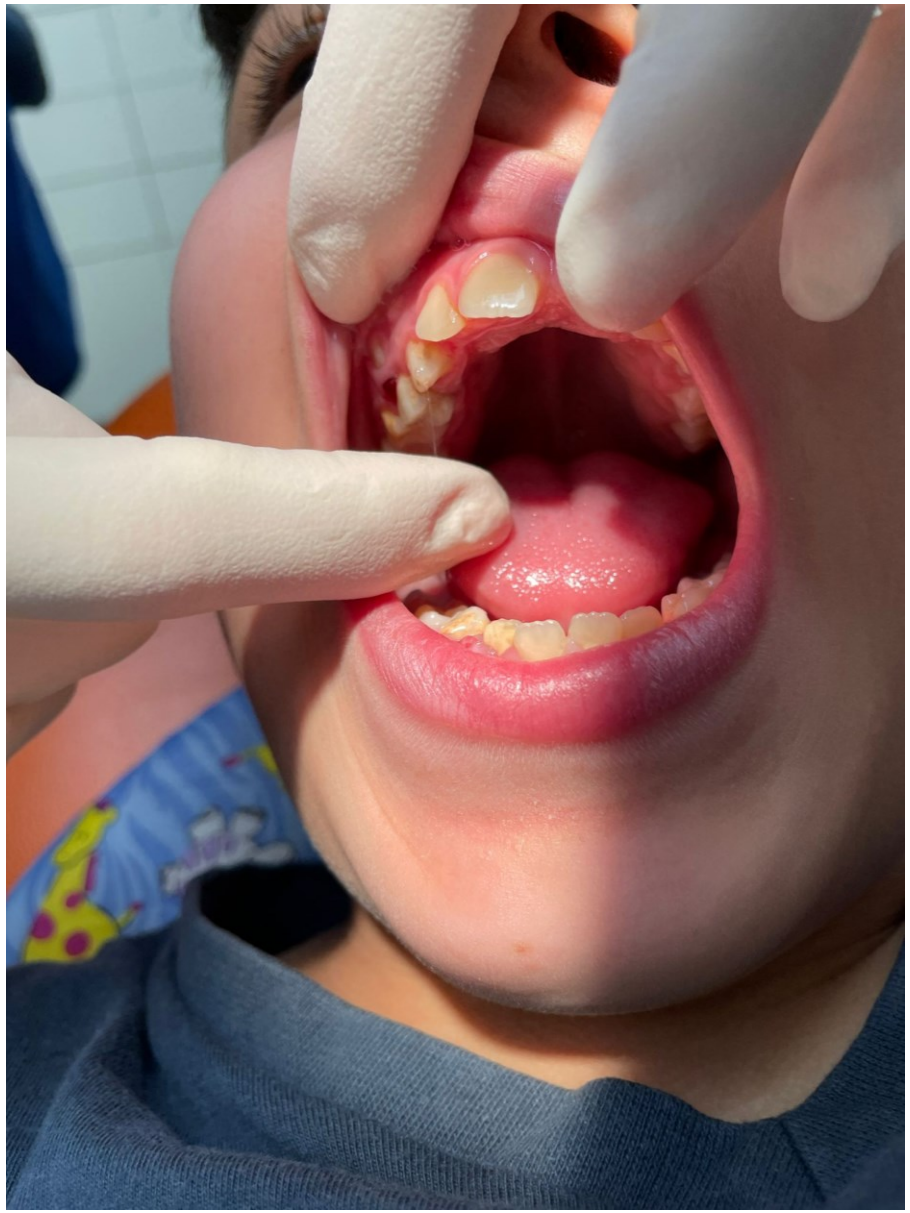
Burosumab and dental health

Dental morbidity is a major health burden in XLH

The development of recurrent abscesses or sinus tracts of the primary and permanent dentition is a frequent sequela

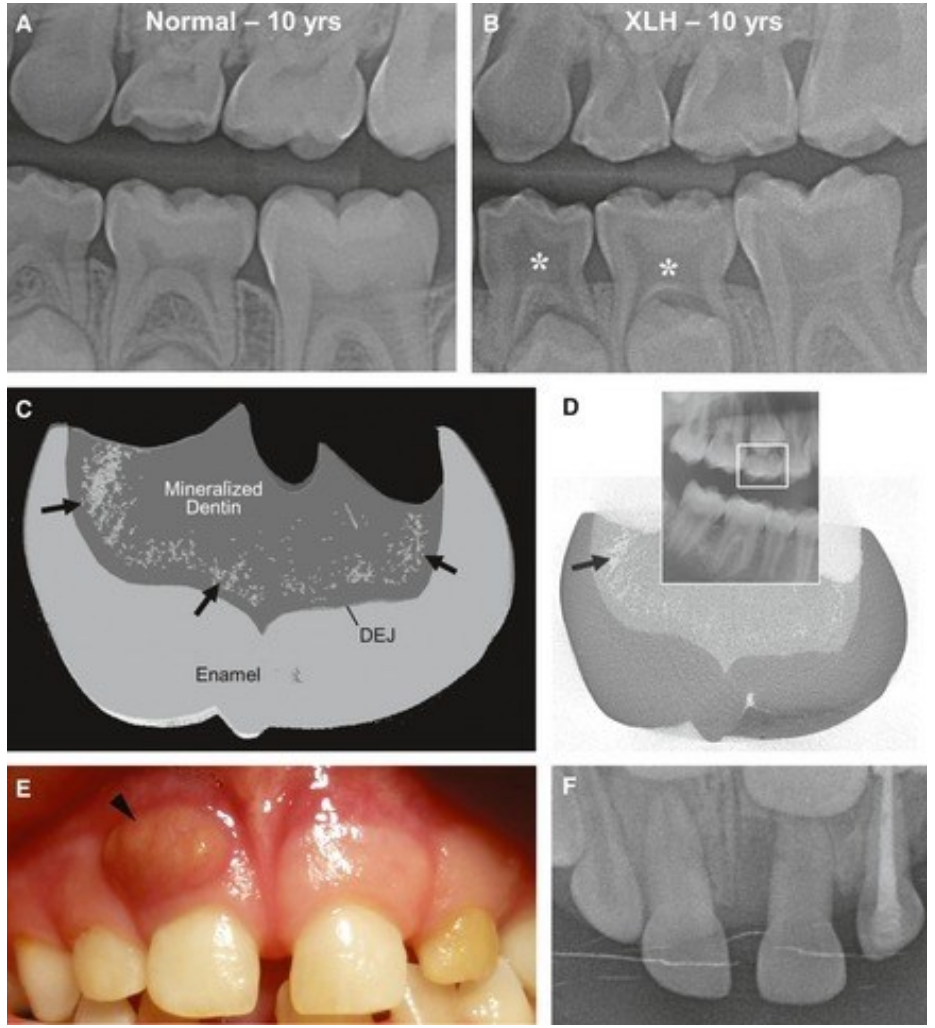


Baroncelli GI et al. Pulp chamber features, prevalence of abscesses, disease severity, and PHEX mutation in X-linked hypophosphatemic rickets J Bone Miner Metab 2021



Distinctive dental morphology in XLH

- Very large pulp chambers
- Thin enamel layer
- Dentinal defects
- Short roots with root resorptions in primary dentition
- Hypoplastic alveolar ridge



Baroncelli GI et al. Pulp chamber features, prevalence of abscesses, disease severity, and PHEX mutation in X-linked hypophosphatemic rickets J Bone Miner Metab 2021

McKee MD, et al. Extracellular matrix mineralization in periodontal tissues: Noncollagenous matrix proteins, enzymes, and relationship to hypophosphatasia and X-linked hypophosphatemia. Periodontol 2000. 2013

frontiers | Frontiers in Endocrinology 2022

Dental health of pediatric patients with X-linked hypophosphatemia (XLH) after three years of burosumab therapy

Rafi Brener[1,2], Leonid Zeitlin[3,4], Yael Lebenthal[4,5] and Avivit Brener[4,5]*

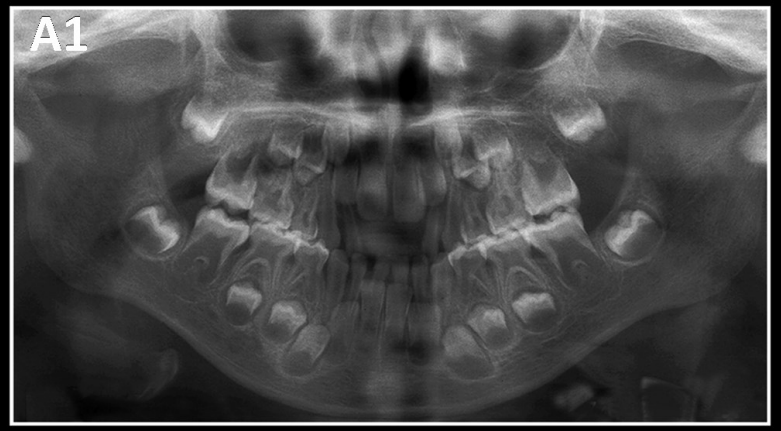
דנה
בי"ח דנה דואק לילדים

Galilee Medical Center

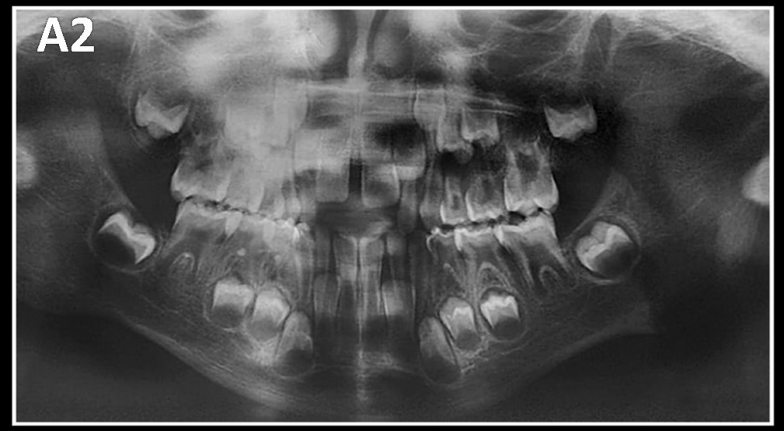
Prospective study
10 XLH patients, age 2.5-16 years at burosumab initiation
10 Sex and age-matched healthy controls

Orthopantomography examinations

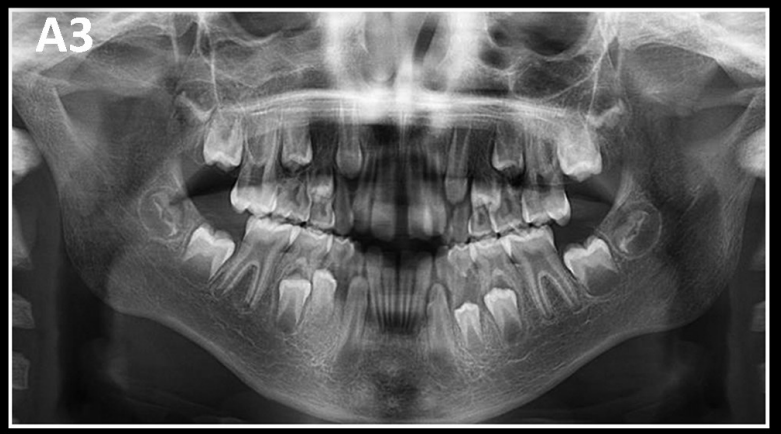
XLH



Baseline (age 5.5 years)

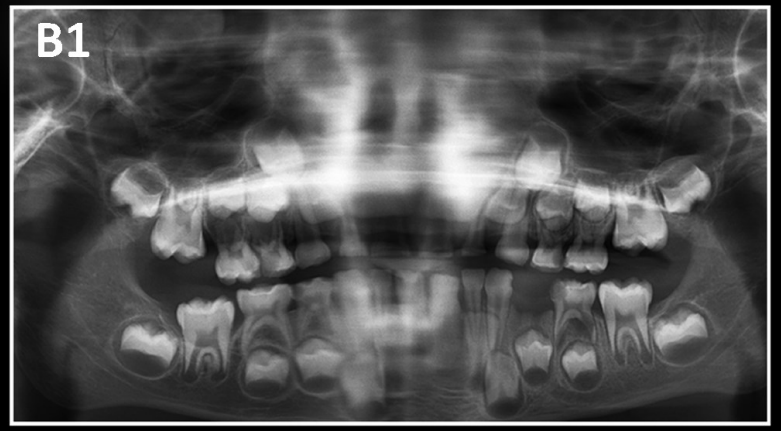


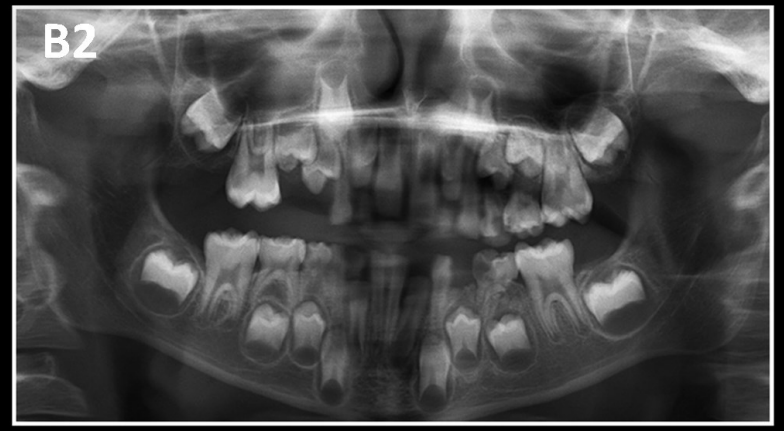
After 1 year

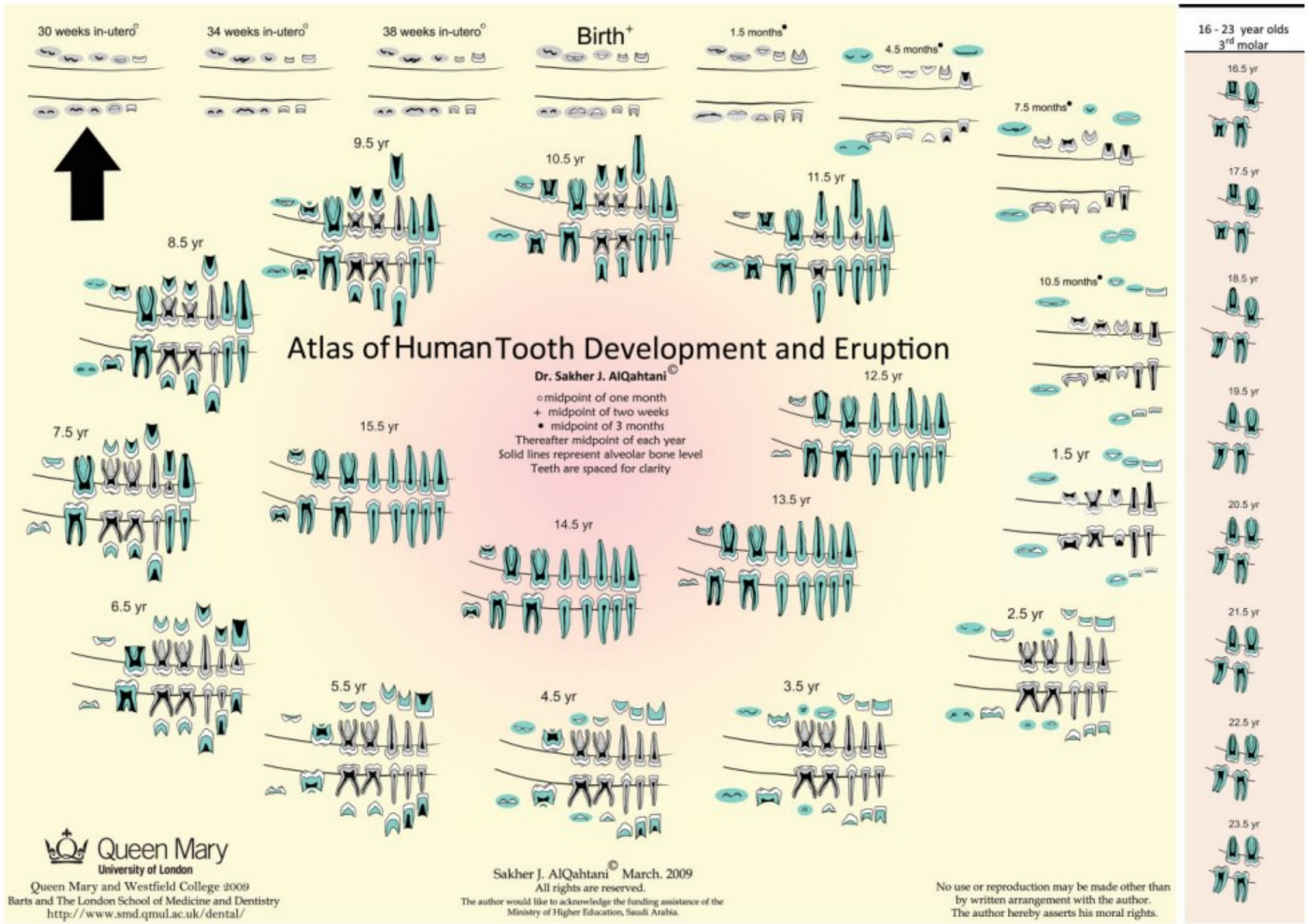


After 3 year

Control







Queen Mary
University of London
Queen Mary and Westfield College 2009
Barts and The London School of Medicine and Dentistry
http://www.smd.qmul.ac.uk/dental/

Sakher J. AlQahtani© March. 2009

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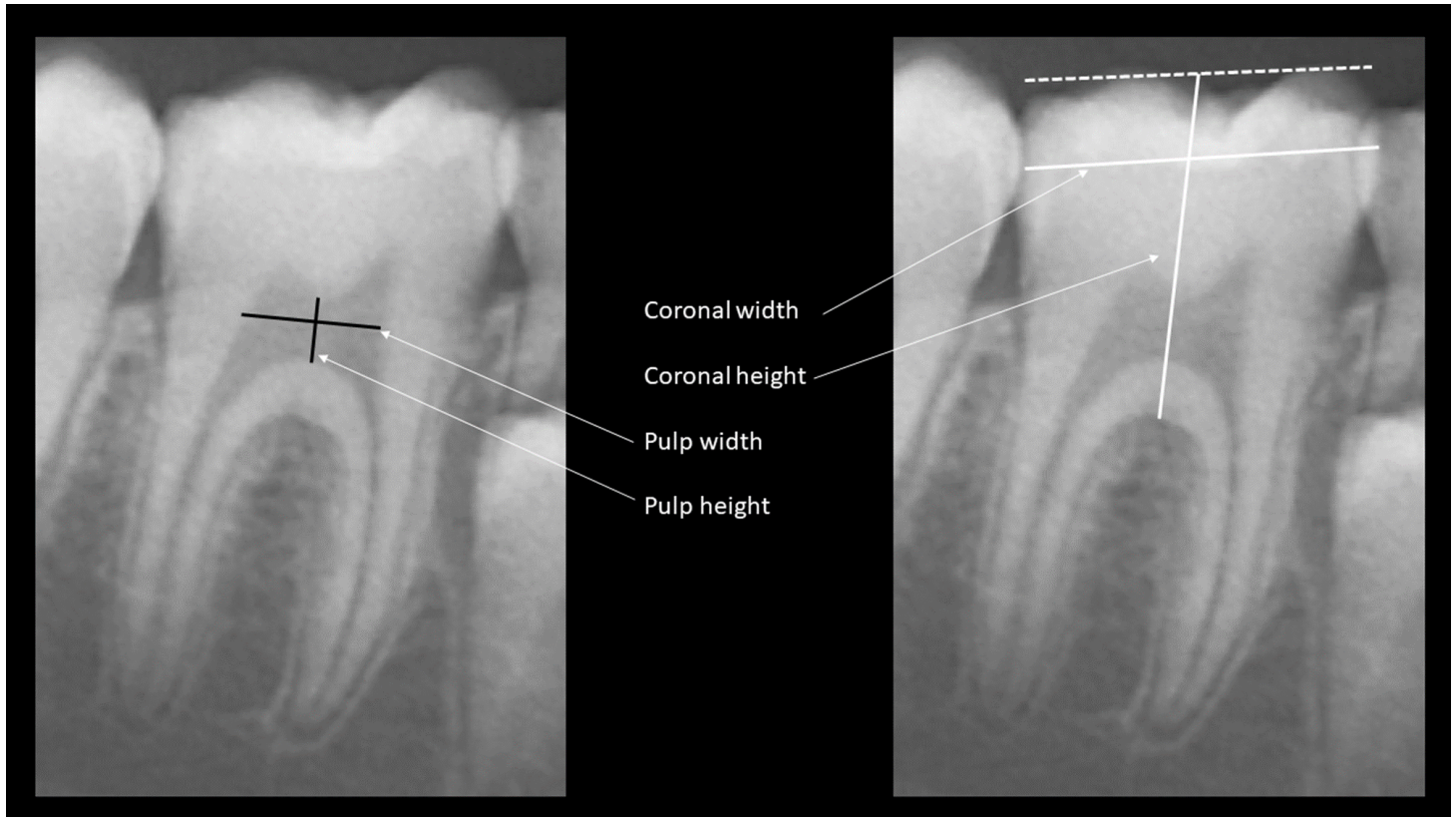
Methods: assessment of dental health and morphology

Ratios were calculated:

- pulp-coronal height ratio (pulp height/coronal height)
- pulp-coronal width ratio (pulp width/coronal width)



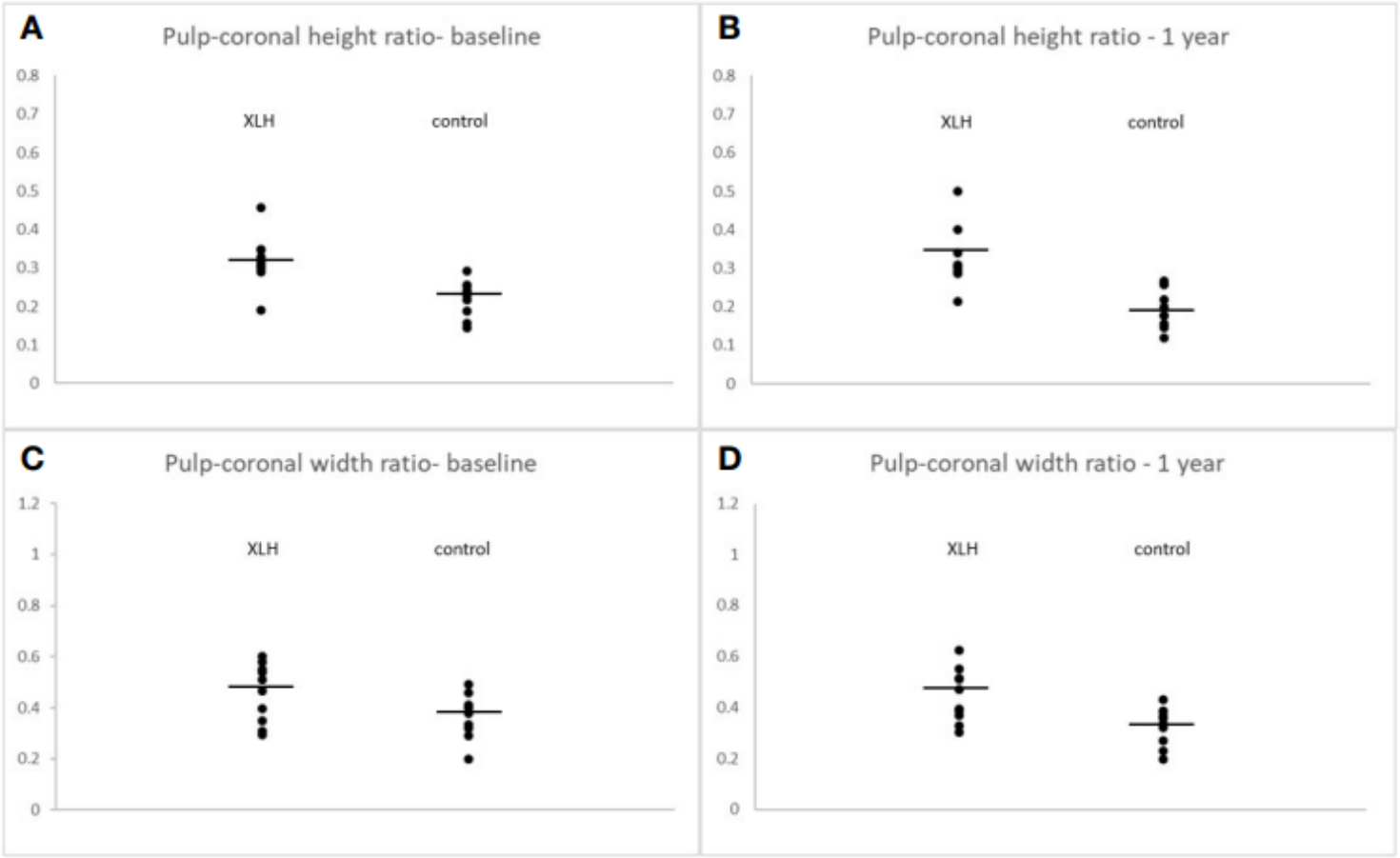


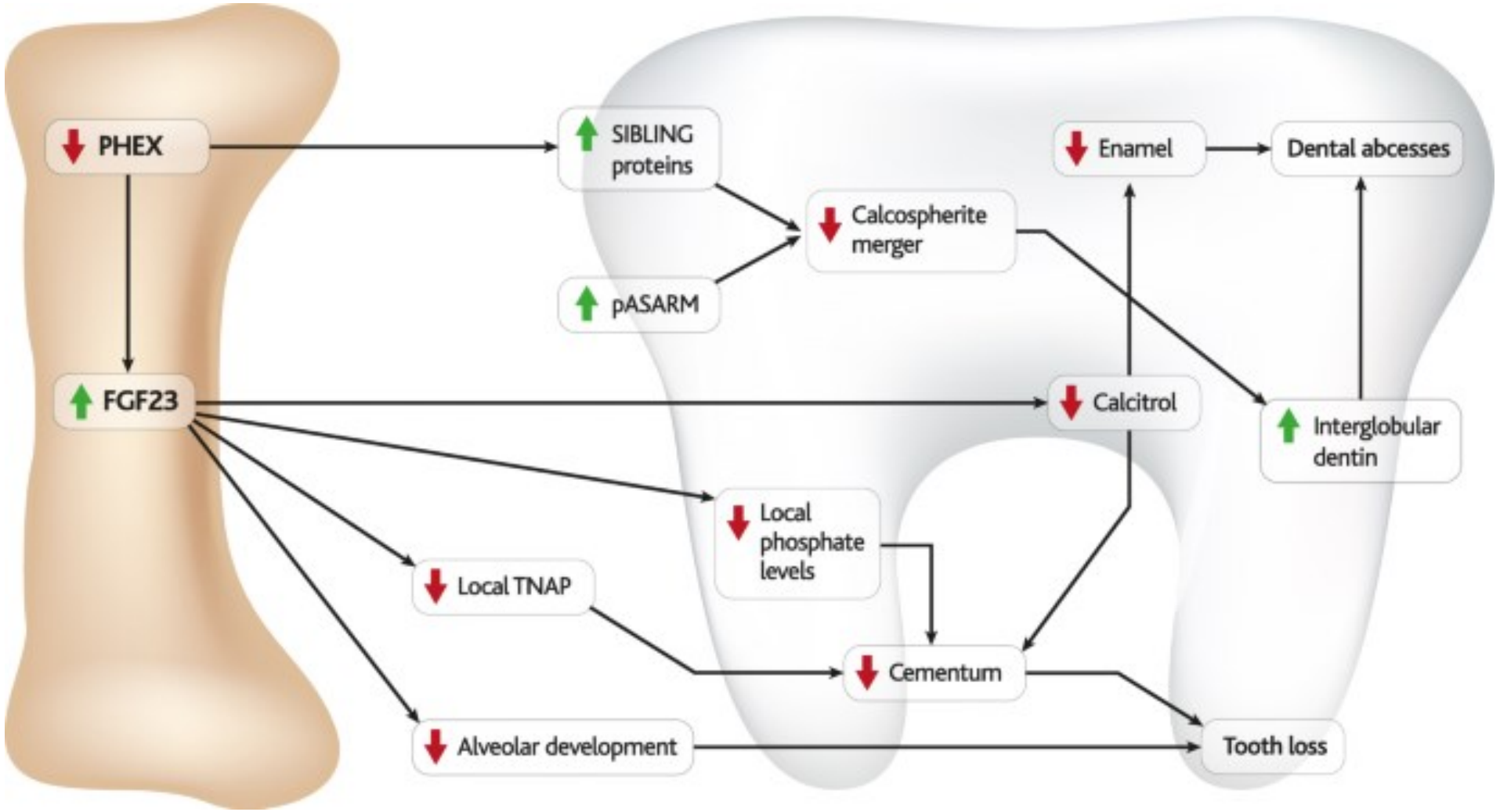
FIGURE 3
Individual values of pulp-coronal height ratios at burosumab initiation **(A)** and after one year **(B)**. Pulp-coronal width ratios at burosumab initiation **(C)** and after one year **(D)** in X-linked hypophosphatemia patients and their controls. Lines indicate mean values. All comparisons were statistically significant at a p value of ≤ 0.05.

TABLE 2 Three-year surveillance of ten burosumab-treated X-linked hypophosphatemia (XLH) patients.

	Baseline	1 year	3 years	P^1	P^2
Age, years	8.8 ± 3.8	9.8 ± 3.8	11.8 ± 3.8		
Burosumab dosage, mg/kg/month	2.09 ± 0.96	2.28 ± 1.20	2.03 ± 1.23	**0.033**	0.952
Dental health					
Patients with dental abscesses	3 (30)	1 (10)	1 (10)	0.582	1
Radiological evaluation					
Rickets severity score, median	3 [1-3]	0 [0-1]	0 [0]	**<0.001**	0.952
Δ bone age, years	-0.27 ± 0.70	-0.13 ± 0.51	-0.07 ± 0.46	0.419	0.087
Δ dental age, years	0.65 ± 0.74	0.47 ± 1.07	0.95 ± 1.35	0.243	0.115
Tooth morphology					
Pulp-coronal height ratio	0.32 ± 0.07	0.33 ± 0.08	0.29 ± 0.05	0.287	**0.009**
Pulp-coronal width ratio	0.48 ± 0.11	0.45 ± 0.11	0.40 ± 0.11	0.482	0.084

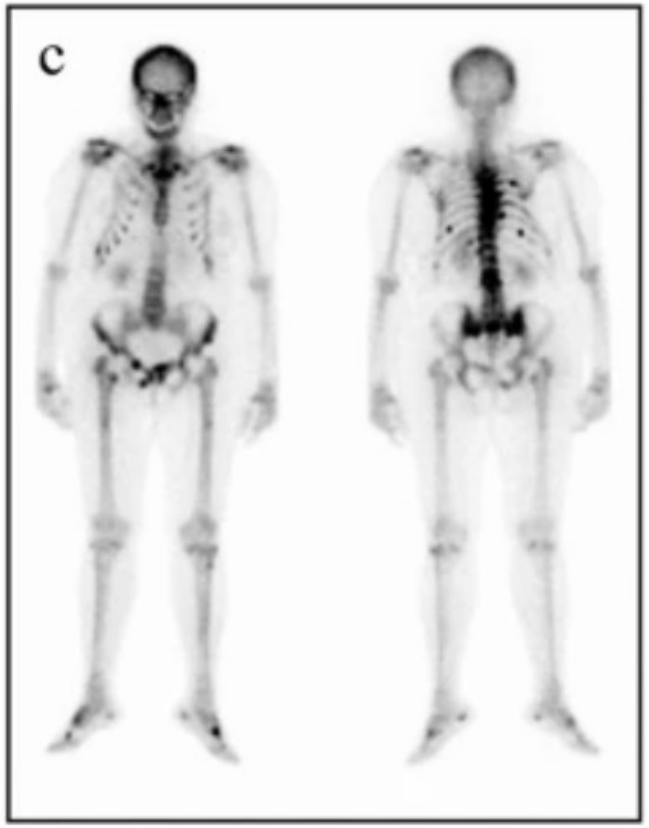
Burosumab treatment normalized phosphate levels, healed rickets and improved linear growth

The dental morphology of XLH patients did not exhibit the desired decrease in the pulp dimensions expected with age

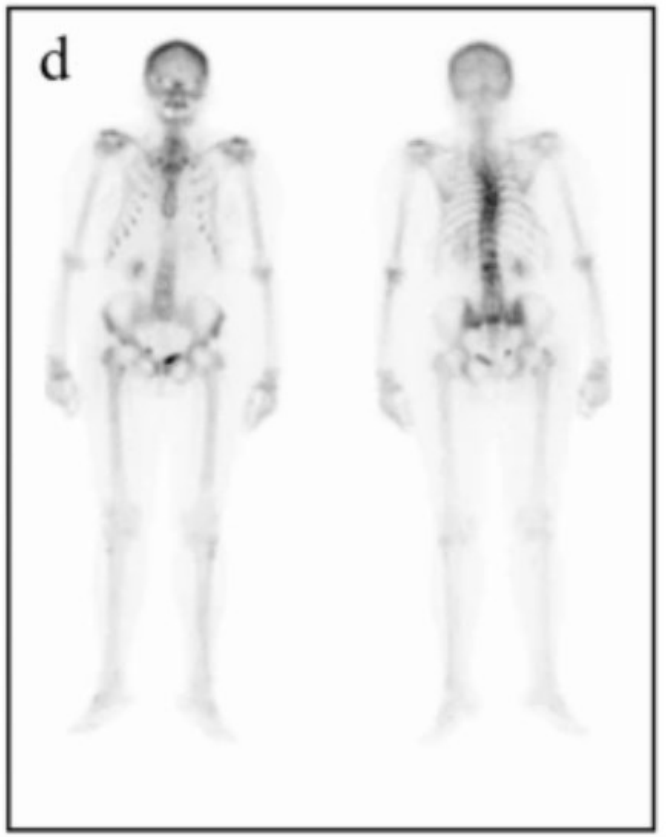


S Beck-Nielsen et al. FGF23 and its role in X-linked hypophosphatemia-related morbidity. Orphanet J of Rare Diseases 2019

Burosumab for the Treatment of Tumor-Induced Osteomalacia (TIO)



Increased tracer uptake at facture sites



After 1 year of burosumab therapy

Crotti C et al. Long-term use of burosumab for the treatment of tumor-induced osteomalacia. Osteoporos Int. 2022

New therapeutic targets for bone disorders

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ORIGINAL ARTICLE

C-Type Natriuretic Peptide Analogue Therapy in Children with Achondroplasia

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