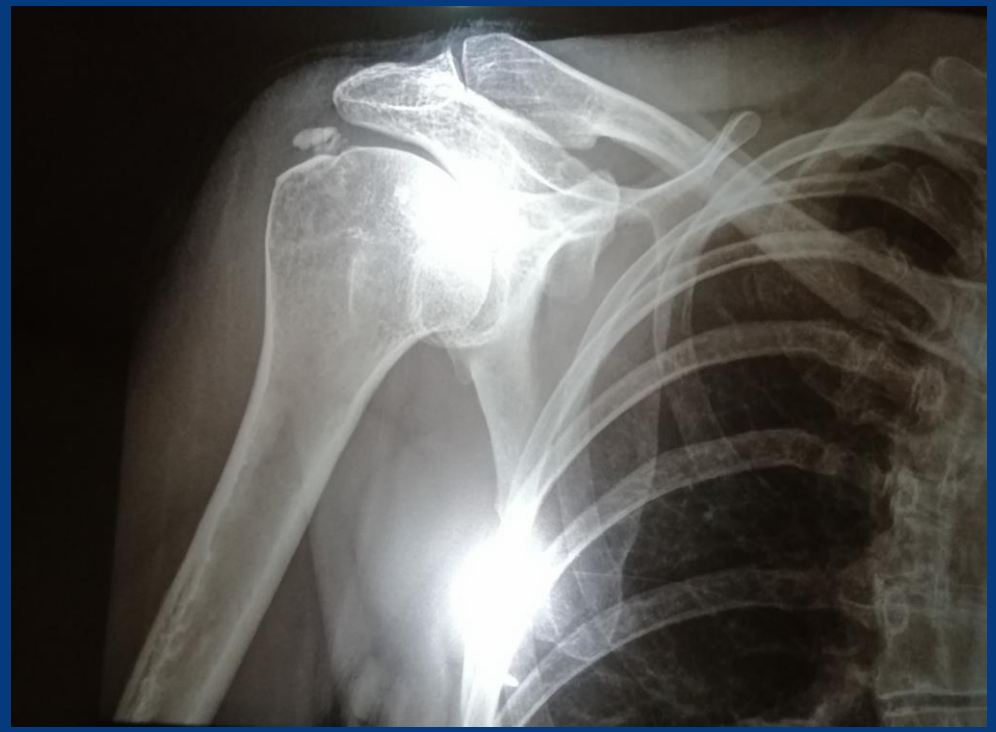
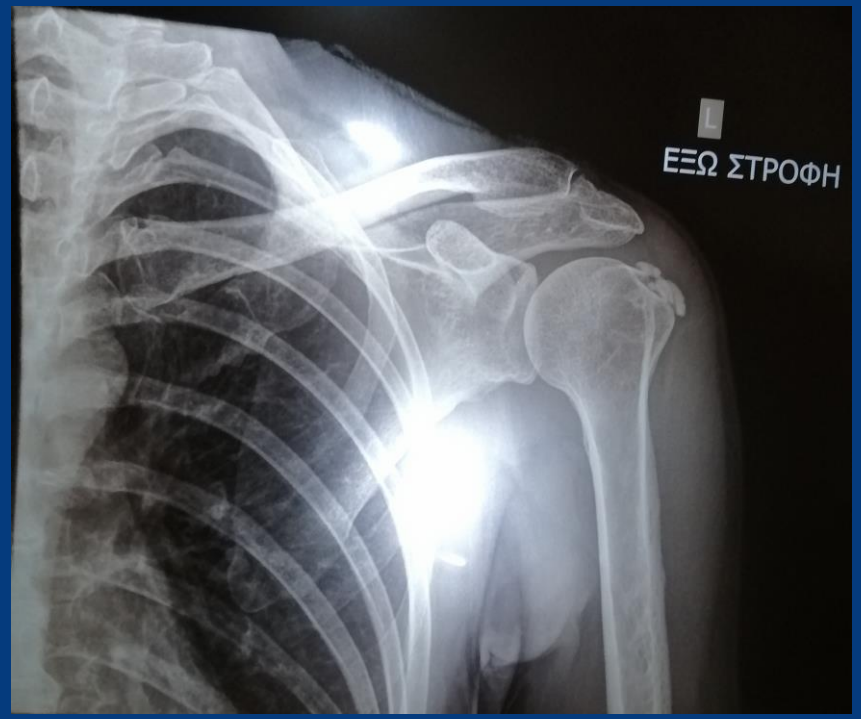
Σπάνια μεταβολικά νοσήματα οστών (Υποφωσφατασία & Υποφωσφοραιμικές ραχίτιδες)

Δρ. Συμεών Τουρνής
Ενδοκρινολόγος
ΕΕΠΜΣ ΕΚΠΑ, Νοσοκομείο ΚΑΤ

Hypophosphatasia



ALP: 20 IU/L (40-105)
B6: 40,2 µg/L (8,7-27,2)



RESULTS	**Pyridoxal-5′-phosphate (PLP – plasma, HPLC)**	**143,5 nmol/l (ref <130); slightly elevated level**
	Phosphoethanolamine (PEA – plasma, HPLC)	0,26 µmol/l (ref <2); normal level
	Phosphoethanolamine (PEA – urine, HPLC)	10,7 mmol/mol creatinine (ref <5); slightly elevated level
	ALPL gene sequencing (DNA - Sanger)	Likely pathogenic variant: p.Pro409Ser; c.1225C>T; heterozygous
SUMMARY	Biochemical and genetic findings are consistent with Mild Adult form of Hypophosphatasia	

The beginning

J.C. Rathbun

"HYPOPHOSPHATASIA"

A New Developmental Anomaly

J. C. RATHBUN, M.D.
TORONTO, CANADA

IN VIEW of the complexities of growth of the various parts of the body, it is not surprising that developmental anomalies occur. Those affecting bone often may be recognized early, and we are all conversant with the well known clinical entities of osteogenesis imperfecta and achondroplasia. Recently a case was referred to the Hospital for Sick Children, Toronto, which belonged in this group of osseous anomalies but presented some unusual findings.

REPORT OF A CASE

J. S., a boy 3 weeks of age, was admitted to the hospital Dec. 6, 1946 and died on Jan. 21, 1947. He was born at full term on Nov. 14, 1946, following a normal seven hour labor. The child cried spontaneously and weighed 9 pounds 11 ounces (4,394.17 Gm.). In spite of fairly well taken breast feedings, the child lost weight steadily, his weight falling to 7 pounds 5 ounces (3,316.89 Gm.), on admission. The mother noted that the child became blue when he cried, and eleven days before admission his cry took on a different quality as though he were in pain. This could be precipitated by handling. Three days before admission he began to have episodes in which he would cry for a minute or two and then coarse, jerking movements of his arms, legs and body occurred, lasting for three to five minutes. The spell would terminate then with a second period of crying lasting two or three minutes. Five such attacks were observed in the three days prior to admission. On the day of admission, a friend noted that the child's head seemed softer than that of an average child.

Feeding History.—The child was breast fed without difficulty.

Family History.—The mother and father were alive and well. There was no familial history of bone diseases in two generations prior to this child. There were no siblings.

Obstetric History.—The mother was a primipara who had an uneventful pregnancy. Her diet was adequate.

Physical Examination.—The patient was a poorly nourished male infant, in no acute distress, with deformities of his wrists and bowing of his legs. The temperature was 99 F. (by rectum).

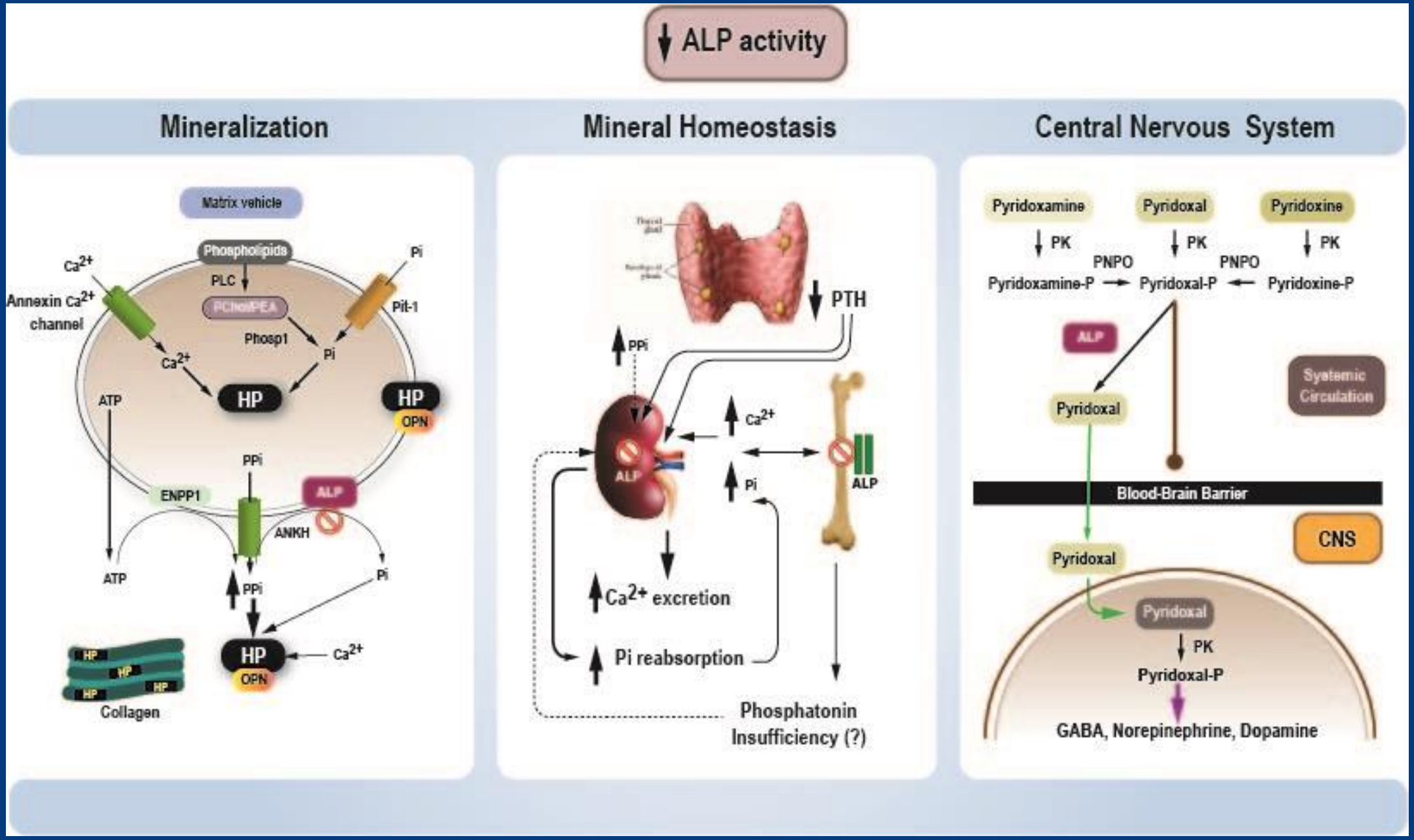
Presented to the Canadian Society for the Study of Diseases of Children, June 7, 1947.

From the Wards and Laboratories of the Hospital for Sick Children, and Department of Pediatrics, University of Toronto, under the direction of Alan Brown, M.D., F.R.C.P. (Lond.).

Dr. J. D. Munn prepared the report on the roentgen examination and Dr. W. L. Donohue assisted with the pathologic specimens.

ΑΛΚΑΛΙΚΗ ΦΩΣΦΑΤΑΣΗ

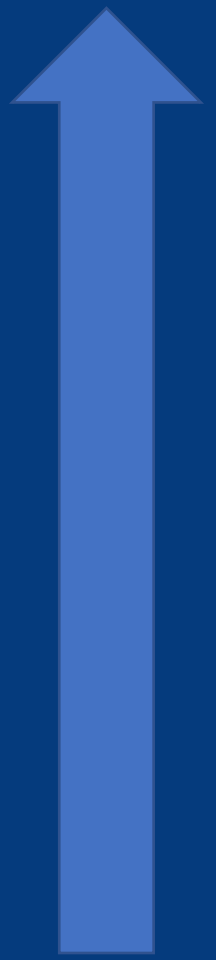
- Καταλύει την υδρόλυση φωσφορικών εστέρων απελευθερώνοντας ανόργανα φωσφορικά (Pi)
- Δρα εξωκυττάρια συνδεδεμένη με την κυτταρική μεμβράνη
- Τέσσερα ισοένζυμα
  - Πλακουντιακό (PLAP) (2q37.1)
  - Γεννητικών κυττάρων (GCAP) (2q37.1)
  - Εντερικό (IAP) (2q37.1)
- 90-98% ομολογία, ομοδιμερή στον ορό και στις μεμβράνες
  - Μη ιστο-ειδικό (TNAP) (1p34-36)
    - Ήπαρ
    - Οστά
    - Νεφρός
    - Δόντια
    - 50% ομολογία με τα ιστο-ειδικά
    - Ομοδιμερή στις μεμβράνες
    - Φυσικά υποστρώματα: PPi, PLP, PEA, pOPN, LPS



Tournis S, Yavropoulou MP, Polyzos SA, Doulgeraki A.
J Clin Med. 2021 Dec 1;10(23):5676. doi: 10.3390/jcm10235676.

Μορφές HPP

1. Περινεογνική [perinatal (OMIM# 241500)]
2. Καλοήθης ενδομήτρια [benign prenatal (OMIM# 264050)]
3. Βρεφική μορφή [infantile (OMIM# 241500)]
4. Παιδική μορφή [childhood (OMIM# 241510)]
   - Ήπια
   - Σοβαρή
5. Μορφή ενηλίκων [adult (OMIM # 146300)]
6. Οδοντοϋποφωσφατασία [odontohypophosphatasia (OMIM#241510)]
7. Φορείς HPP



HPP

- Η πρωιμότερη εμφάνιση σχετίζεται κατά κανόνα με βαρύτερη νόσο και χειρότερη πρόγνωση
- Οι πρώιμες μορφές μεταβιβάζονται με σωματικό υπολειπόμενο, ενώ οι όψιμες ηπιότερες μορφές με σωματικό επικρατούντα ή υπολειπόμενο χαρακτήρα.
- Μεγάλη ποικιλομορφία στις εκδηλώσεις και στη βαρύτητα αυτών ακόμη και στην ίδια οικογένεια

HPP severity

Odonto HPP

Presentation: at any age
In children: before 5 yrs
painless loss of deciduous teeth with root intact
First: Lower incisors
Otherwise normal

Adult HPP

Presentation: middle age
Muscle weakness
Skeletal/joint pain
Loss of secondary dentition
Metatarsal stress fractures
Delayed fracture healing
Femoral pseudofractures, BME (Hip, Knee, Feet)
Chondrocalcinosis, PPi arthropathy, calcific periarthritis

Childhood HPP

Presentation: after 6 months
Loss of primary teeth
Muscle Weakness
Skeletal pain
Rickets (bowed legs, knock knees)
Craniosynostosis
Symptoms might improve in young adult life

Infantile HPP

Presentation: before 6 months
Poor feeding, Weakness
Delayed motor milestones
Rickets
Craniosynostosis
B6-dependent seizures
Thoracic deformity
Intracranial hemorrhage
Hypercalcemia/uria
Mortality:50%

Perinatal HPP

Presentation: in utero
Profound hypomineralization
Short deformed limbs
Hypoplastic lungs
Intracranial hemorrhage
Seizures
Fever
Anemia
Mortality≈ 100%

When to suspect HPP

When to suspect HPP

- Defective bone mineralization
  - Nontraumatic/recurrent fractures
  - Stress fractures of metatarsals (foot pain)
  - Delayed fracture healing
- Defective tooth mineralization
  - Premature loss of secondary dentition
  - Short roots, enamel hypoplasia, severe dental caries, and alveolar bone loss
- Laboratory
  - Hypophosphatasaemia, i.e., persistently low serum ALP (upon repeated tests), after exclusion of other known causes
  - Increased levels of ALP substrates (PLP, PEA; PPI if available)
- Radiology/ultrasound
  - Chondrocalcinosis
  - Enthesopathies
  - Calcific periarthritis

Bianchi ML, et al Osteoporosis International 2020

Diagnosis

- History, physical examination.
- Persistently low ALP (age and sex-specific reference range)
- Low ALP in first degree relatives
- Radiological findings (perinatal, infantile, childhood, adults-CCPD [knees,pelvis,wrist,hands]-calcific periarthritis [shoulder,trochanter])
- Lab
  - ↑ serum PLP (B6)
  - ↑ ePEA serum / urine: low sensitivity and specificity
  - ↑ PPi serum/urine
  - ↑ sCa, uCa
  - PTH: ↔↓
  - 25 (OH)D: ↔
  - 1.25 (OH)2D: ↔↓
  - P ↔/ ↑ , ↑ TMP/GFR
- TNSALP mutation (> 380)
  - missense (80%)
  - nonsense
  - donor splice site mutations
  - frame-shift deletions
- Biopsy

Διαφορική Διάγνωση

- Cardiac bypass surgery
- **Coeliac Disease**
- Clofibrate
- Steroids, BSP, Denosumab
- Cleidocranial dysplasia
- Cushing syndrome
- **Hypothyroidism**
- Improperly collected blood (oxalate, EDTA)
- **Inappropriate reference range**
- Massive transfusion
- Milk-alkali syndrome
- **Multiple myeloma**
- OI type II
- Pernicious or profound anemia
- Radioactive heavy metals
- Starvation
- Vitamin C deficiency
- Vitamin D intoxication
- Wilson disease
- Zn or Mg deficiency

Whyte M. Nature Rev Endo 2016

Αντιμετώπιση

- Υποστηρικτική
  - Μηχανικός αερισμός
  - B6 για B6-dependent seizures
  - Κρανιοσυνοστέωση: Κρανιοτομή
  - Οδοντιατρική παρακολούθηση
  - NSAIDs (ναπροξένη)
- Αποφυγή υπερβολικής διόρθωσης υποβιταμίνωσης D, πρόσληψης ασβεστίου, διφωσφονικών, Dmab
- Θεραπευτικά
  - Θεραπεία ενζυμικής υποκατάστασης με asfotase alfa [Enzyme Replacement Therapy (ERT) with Recombinant, mineral-targeted, human TNSALP]
  - Τεριπαρατίδη

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Enzyme-Replacement Therapy in Life-Threatening Hypophosphatasia

Michael P. Whyte, M.D., Cheryl R. Greenberg, M.D., Nada J. Salman, M.D., Michael B. Bober, M.D., Ph.D., William H. McAlister, M.D., Deborah Wenkert, M.D., Bradley J. Van Sickle, M.D., Ph.D., Jill H. Simmons, M.D., Terence S. Edgar, M.D., Martin L. Bauer, M.D., Mohamad A. Hamdan, M.D., Nick Bishop, M.D., Richard E. Lutz, M.D., Mairead McGinn, M.D., Stanley Craig, M.D., Jean N. Moore, M.D., John W. Taylor, D.O., Robert H. Cleveland, M.D., William R. Cranley, M.D., Ruth Lim, M.D., Tom D. Thacher, M.D., Jill E. Mayhew, P.T., Matthew Downs, M.P.H., José Luis Millán, Ph.D., Alison M. Skrinar, M.P.H., Philippa Crina, Ph.D., and Hal Landy, M.D.

From the Center for Metabolic Bone Disease and Molecular Research, Shriners Hospital for Children (M.P.W., D.W.), the Division of Bone and Mineral Diseases, Washington University School of Medicine at Barnes–Jewish Hospital (M.P.W.), and Mallinckrodt Institute of Radiology, St. Louis Children's Hospital at Washington University School of Medicine (W.H.M.) — all in St. Louis; the University of Manitoba and Winnipeg Regional Health Authority, Winnipeg, Canada (C.R.G.); Tawam Hospital, Al Ain, United Arab Emirates (N.J.S., M.A.H.); Alfred I. DuPont Hospital for Children, Wilmington, DE (M.B.B.); Vanderbilt Children's Hospital, Nashville (B.J.V.S., J.H.S.); Prevea Health Clinic (T.S.E., J.W.T.) and St. Vincent's Hospital (J.W.T.) — both in Green Bay, WI; University of Arkansas for Medical Sciences, College of Medicine, Little Rock (M.L.B.); Sheffield Children's Hospital, Sheffield (N.B.), and Royal Belfast Hospital for Sick Children, Belfast (M.M., S.C.) — both in the United Kingdom; University of Nebraska Medical Center, Omaha (R.E.L.); St. John's Hospital, Springfield, MO (J.N.M.); Children's Hospital Boston (R.H.C.), Boston Medical Center (W.R.C.), and Massachusetts General Hospital (R.L.) — all in Boston; Mayo Clinic, Rochester, MN (T.D.T.); Enobia Pharma, Montreal (J.E.M., A.M.S., P.C., H.L.); Statistics Collaborative, Washington, DC (M.D.); and Sanford–Burnham Medical Research Institute, La Jolla, CA (J.L.M.). Address reprint requests to Dr. Whyte at Shriners Hospital for Children, 2001 S. Lindbergh Blvd., St. Louis, MO 63131, or at mwhyte@shrinenet.org.

This article (10.1056/NEJMoa1106273) was updated on March 8, 2012.

N Engl J Med 2012;366:904-13.

ABSTRACT

BACKGROUND

Hypophosphatasia results from mutations in the gene for the tissue-nonspecific isozyme of alkaline phosphatase (TNSALP). Inorganic pyrophosphate accumulates extracellularly, leading to rickets or osteomalacia. Severely affected babies often die from respiratory insufficiency due to progressive chest deformity or have persistent bone disease. There is no approved medical therapy. ENB-0040 is a bone-targeted, recombinant human TNSALP that prevents the manifestations of hypophosphatasia in Tnsalp knockout mice.

METHODS

We enrolled infants and young children with life-threatening or debilitating perinatal or infantile hypophosphatasia in a multinational, open-label study of treatment with ENB-0040. The primary objective was the healing of rickets, as assessed by means of radiographic scales. Motor and cognitive development, respiratory function, and safety were evaluated, as well as the pharmacokinetics and pharmacodynamics of ENB-0040.

RESULTS

Of the 11 patients recruited, 10 completed 6 months of therapy; 9 completed 1 year. Healing of rickets at 6 months in 9 patients was accompanied by improvement in developmental milestones and pulmonary function. Elevated plasma levels of the TNSALP substrates inorganic pyrophosphate and pyridoxal 5′-phosphate diminished. Increases in serum parathyroid hormone accompanied skeletal healing, often necessitating dietary calcium supplementation. There was no evidence of hypocalcemia, ectopic calcification, or definite drug-related serious adverse events. Low titers of anti–ENB-0040 antibodies developed in four patients, with no evident clinical, biochemical, or autoimmune abnormalities at 48 weeks of treatment.

CONCLUSIONS

ENB-0040, an enzyme-replacement therapy, was associated with improved findings on skeletal radiographs and improved pulmonary and physical function in infants and young children with life-threatening hypophosphatasia. (Funded by Enobia Pharma and Shriners Hospitals for Children; ClinicalTrials.gov number, NCT00744042.)

Design: Open label study

Duration: 1 yr. (with extension)

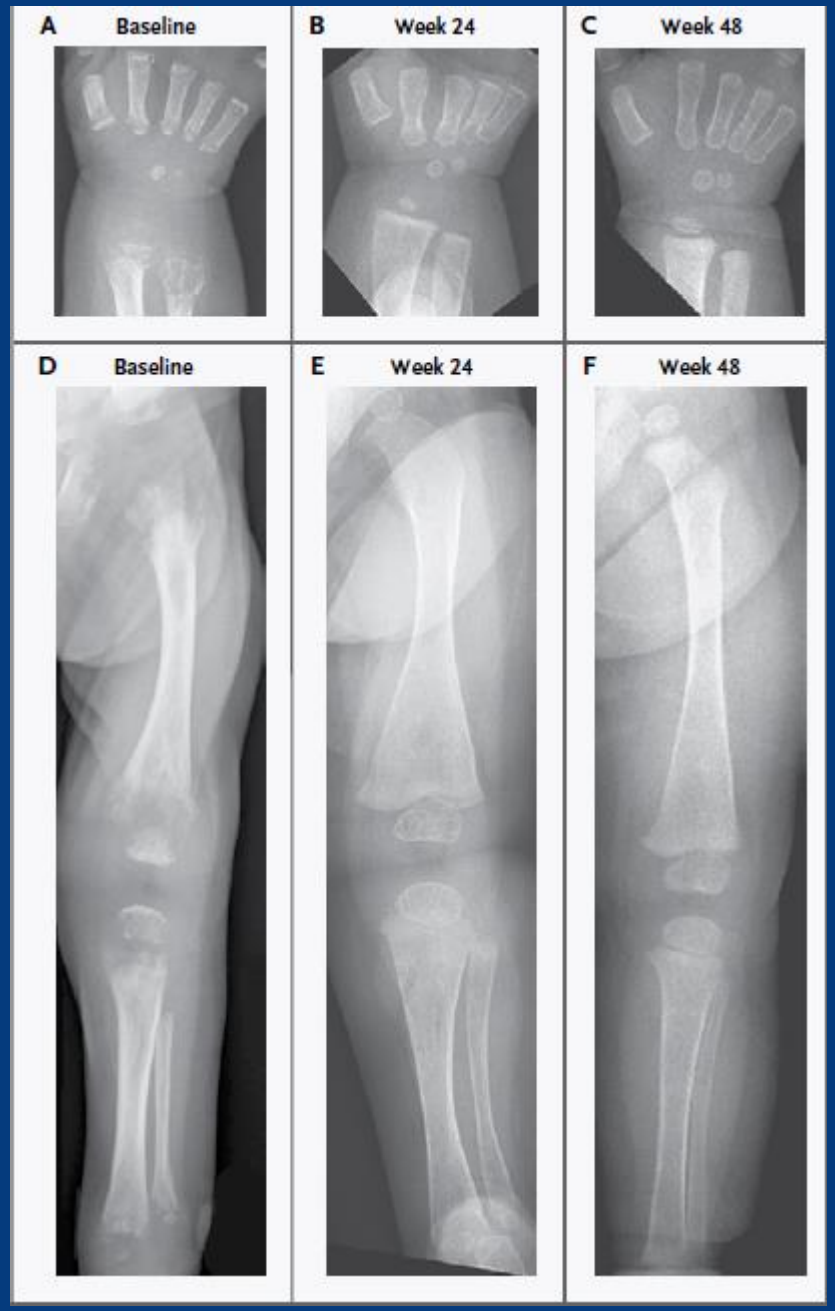
Pts: 11 pts with perinatal (5) or infantile (6) HPP

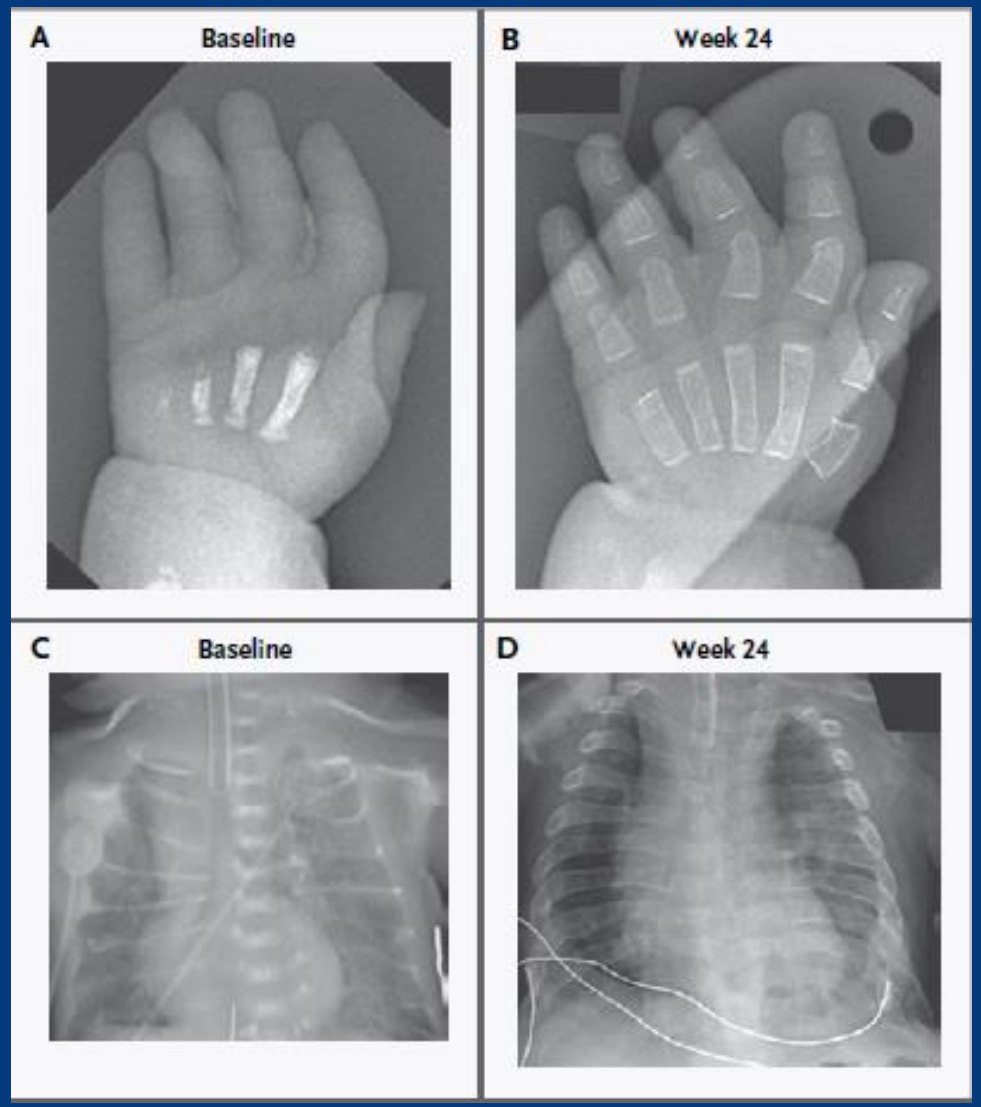
Age: < 3yrs

Dose: Infusion at a dose of 2 mg per kilogram, followed by sbc 1 mg/kg 3 times/ week (up to 3 mg/kg if no response- total 9 mg/kg/wk.).

Primary EP: change in the skeletal manifestations of HPP

Other EP: safety, tolerability


A Baseline
B Week 24
C Week 48
D Baseline
E Week 24
F Week 48


A Baseline
B Week 24
C Baseline
D Week 24

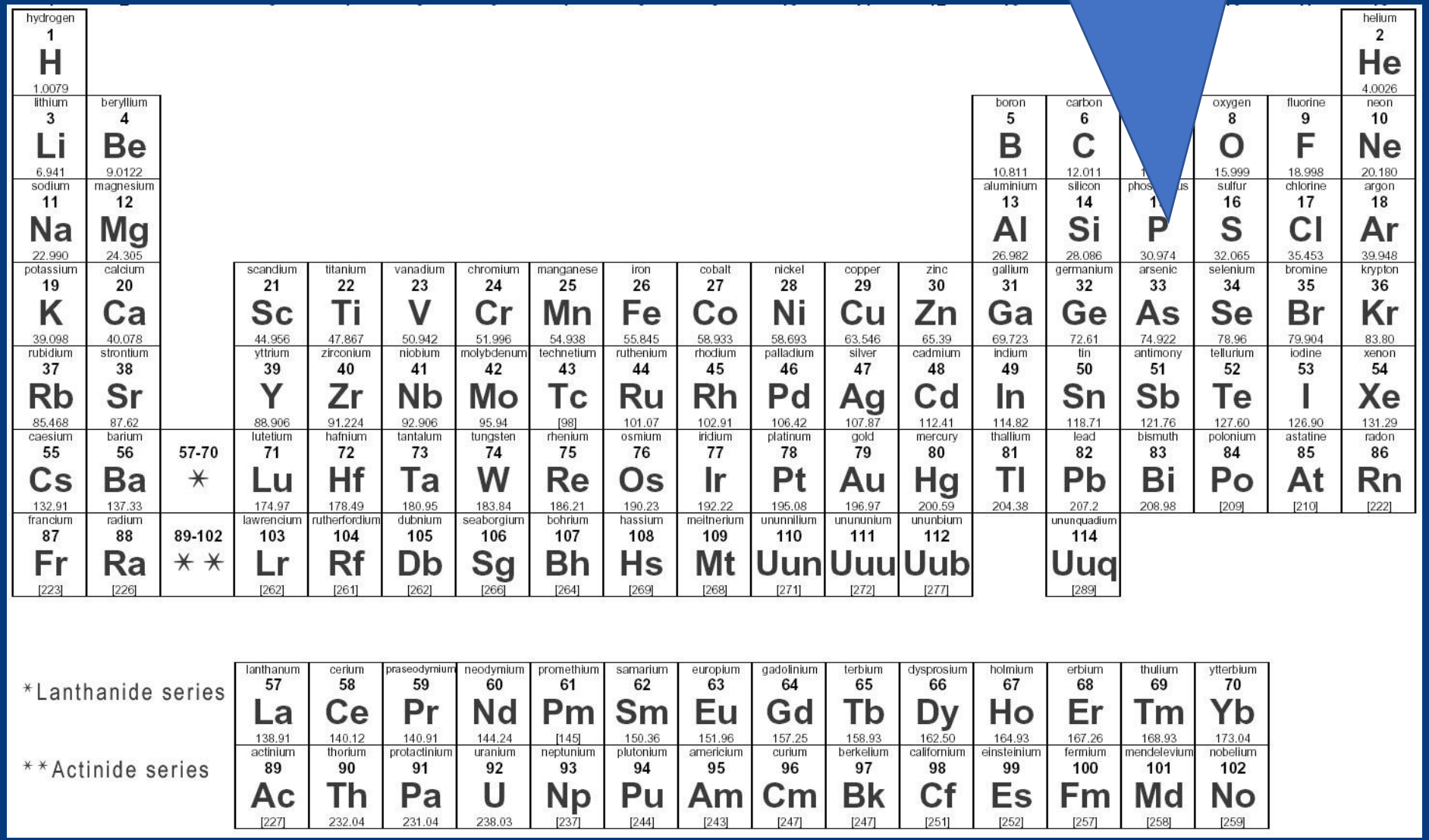
Indications for ERT in adults

1. Osteomalacia and complications of osteomalacia
2. Pseudofractures.
3. Intractable musculoskeletal pain requiring or unresponsive to opioids.
4. Presence of chondrocalcinosis with intractable pain
5. Major osteoporotic fractures.
6. Delayed or incomplete fracture healing.
7. Individuals with significant impairment in function with impaired gait and mobility.

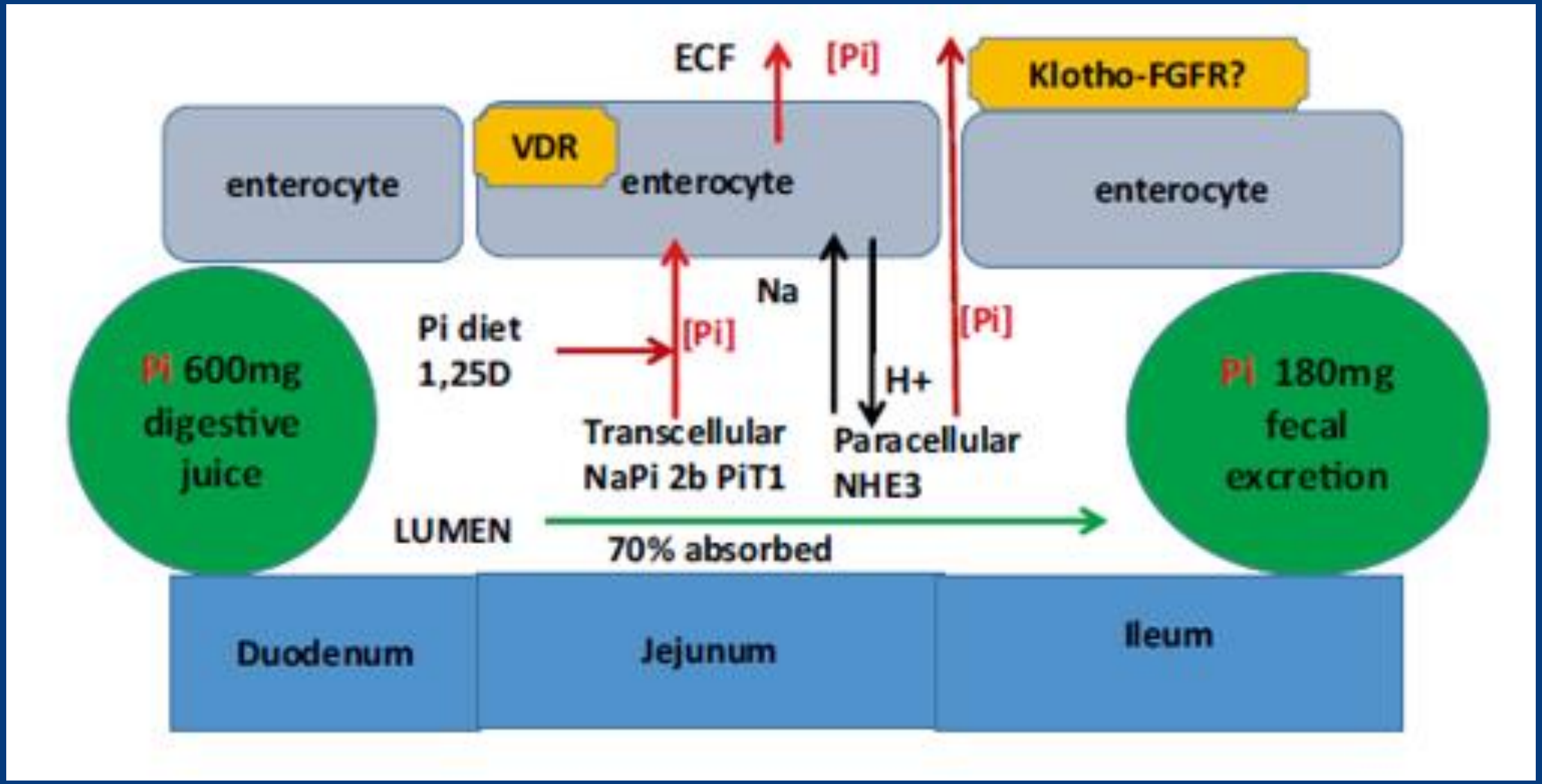
Ost Int 2019, Canadian Guidelines

ΙΣΤΟΡΙΚΗ ΑΝΑΔΡΟΜΗ

1. Ανακαλύφθηκε: 1669/Brand
2. Ετυμολογία: Φως+Φέρω

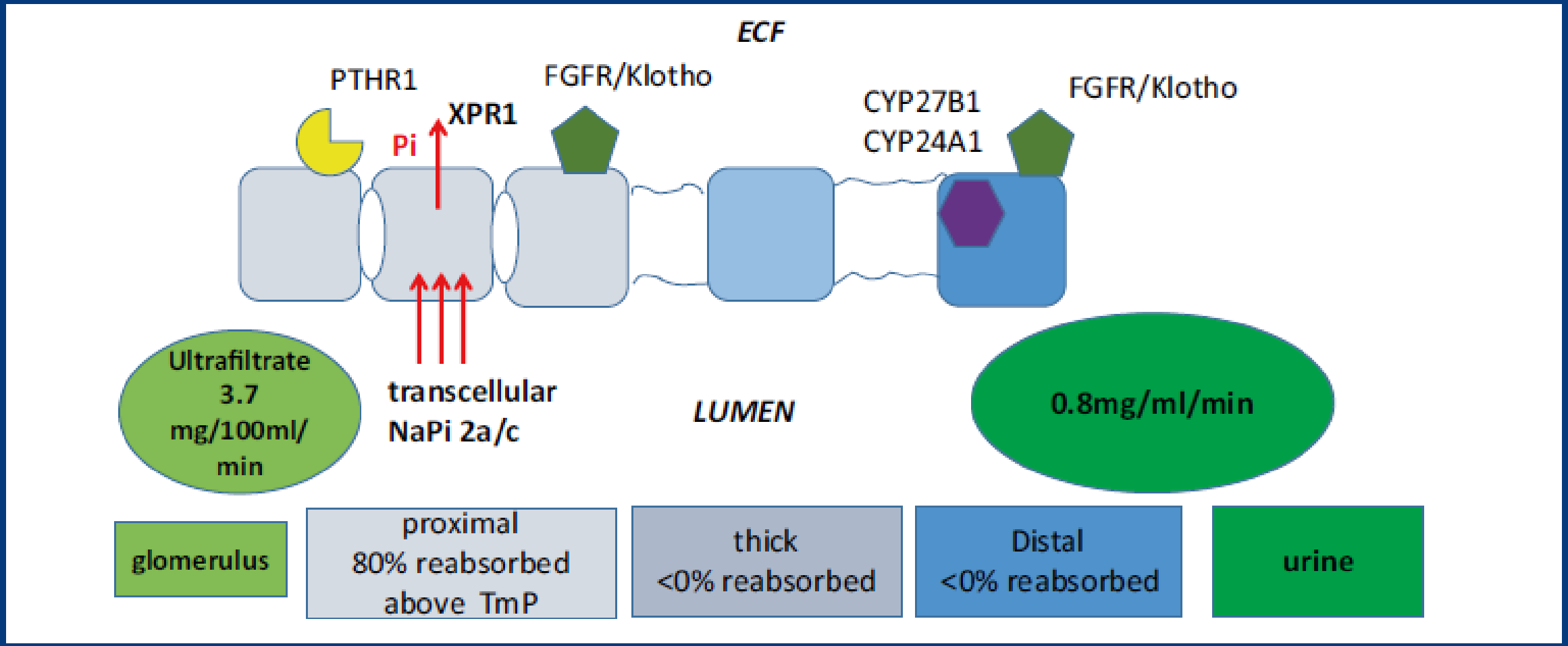


Εντερική διακίνηση φωσφόρου

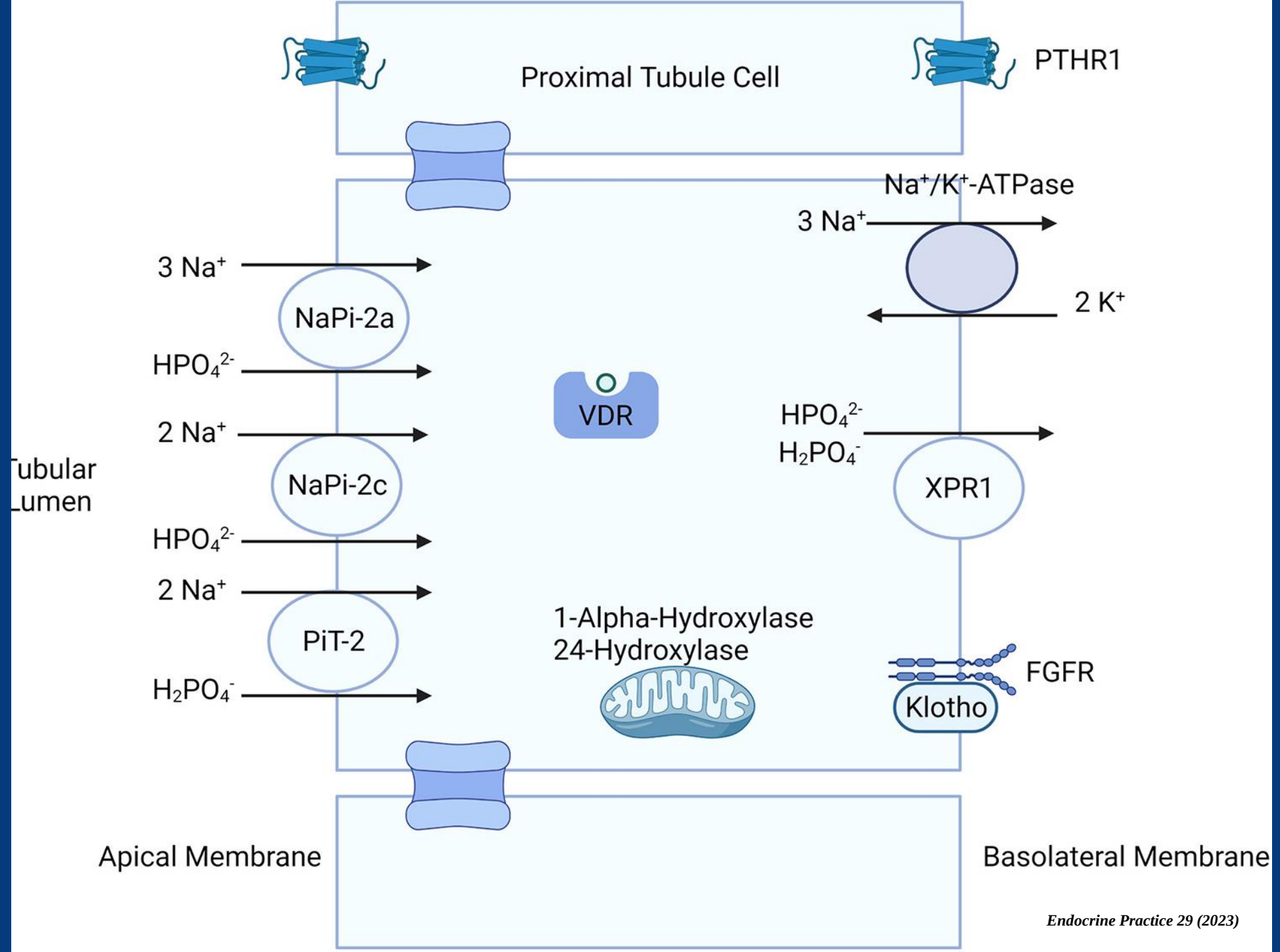


Peacock M. CTI 2020

Νεφρική διακίνηση φωσφόρου



Peacock M. CTI 2020



Endocrine Practice 29 (2023)

JOURNAL OF BONE AND MINERAL RESEARCH
Volume 4, Number 4, 1989
Mary Ann Liebert, Inc., Publishers

FGF23 dependent Hypophosphatemia

Parabiosis Suggests a Humoral Factor Is Involved in *X*-Linked Hypophosphatemia in Mice

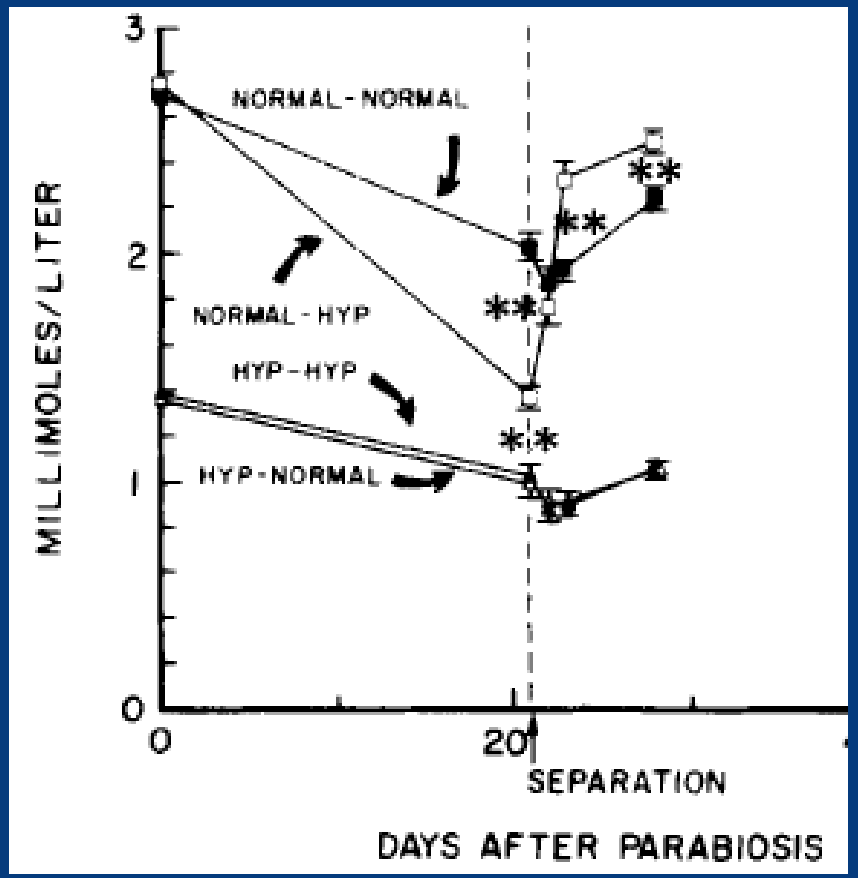


TABLE 1. EFFECT OF PARABIOSIS ON PLASMA MINERALS AND SKELETAL GROWTH IN NORMAL AND *Hyp* MICE 3 WEEKS AFTER SURGERY[a]

	Normal to normal	*Normal to* Hyp		Hyp *to* Hyp
		Normal	Hyp	
Presurgery data				
Plasma				
Phosphate	2.88 ± 0.04 (30)	2.84 ± 0.05 (17)	1.44 ± 0.05 (17)[c]	1.43 ± 0.03 (30)[b]
Physical data				
Body weight	12.1 ± 0.4 (30)	12.1 ± 0.5 (17)	11.3 ± 0.4 (17)	11.2 ± 0.3 (30)
Body length	72.1 ± 0.8 (30)	71.9 ± 1.1 (17)	69.0 ± 0.8 (17)[c]	69.5 ± 0.6 (30)[b]
Tail length	64.0 ± 0.7 (30)	64.6 ± 0.8 (17)	56.3 ± 0.6 (17)[c]	56.6 ± 0.4 (30)[b]
3 Weeks after parabiosis				
Plasma				
Phosphate	2.33 ± 0.05 (28)	1.66 ± 0.06 (15)[b]	1.54 ± 0.06 (15)[d]	1.35 ± 0.04 (25)[b]
Calcium	2.10 ± 0.02 (28)	2.02 ± 0.03 (16)[b]	2.01 ± 0.03 (15)	1.99 ± 0.02 (25)[b]
$1,25\text{-}(OH)_2\text{-}D$	78 ± 32 (6)	35 ± 20 (3)	37 ± 22 (3)	69 ± 23 (6)

TUMOR-INDUCED OSTEOMALACIA — UNVEILING A NEW HORMONE

PHOSPHATE plays a critical part in the regulation of cell metabolism, and phosphate homeostasis is closely regulated in normal humans. Indeed, like serum calcium, serum phosphate is maintained within a narrow range of values, and people with abnormal concentrations may have a predisposition to life-threatening conditions, such as hemolysis, myopathy, hypocalcemia, and nephrocalcinosis.

The principal organ that regulates phosphate homeostasis is the kidney. Regulation is accomplished partly through variation in glomerular filtration of phosphate but primarily through variation in renal tubular reabsorption of phosphate. These variations are detectable within 24 hours after a change in dietary phosphate intake and even more rapidly after a sudden change in the serum phosphate concentration due to an event such as rhabdomyolysis. The mechanism (or mechanisms) underlying adaptation to changes in dietary phosphate intake is unclear. Moreover, although sudden alterations in phosphate homeostasis are ascribed to changes in parathyroid hormone secretion, this explanation is unlikely, since an increase in parathyroid hormone secretion results in both increased mobilization of phosphate from bone and increased urinary phosphate excretion, thus exerting opposite effects on the serum phosphate concentration and having a limited influence on phosphate homeostasis. Therefore, there has been speculation that a separate phosphate-regulating hormone

esses remain unknown, further studies of genetic disorders and oncogenic osteomalacia should soon provide the means to address these issues. Indeed, Cai et al.[1] may have made a small but very important step in the discovery of "phosphatonin."

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MICHAEL J. ECONS, M.D.
MARC K. DREZNER, M.D.

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NEJM 1994

letter

Autosomal dominant hypophosphataemic rickets is associated with mutations in *FGF23*

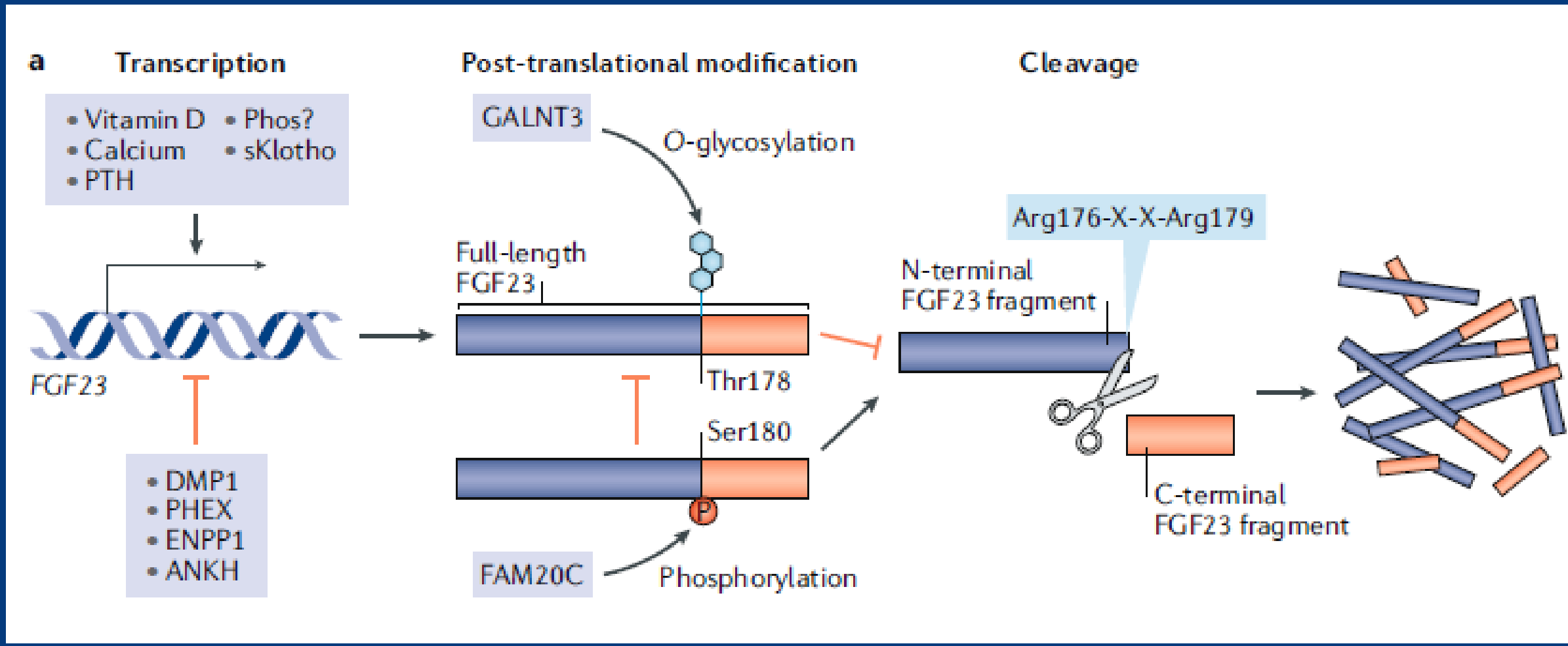
The ADHR Consortium

Proper serum phosphate concentrations are maintained by a complex and poorly understood process. Identification of genes responsible for inherited disorders involving disturbances in phosphate homeostasis may provide insight into the pathways that regulate phosphate balance. Several hereditary disorders of isolated phosphate wasting have been described, including X-linked hypophosphataemic rickets[1] (XLH), hypophosphataemic bone disease[2] (HBD), hereditary hypophosphataemic rickets with hypercalciuria[3] (HHRH) and autosomal dominant hypophosphataemic rickets[4,5] (ADHR). Inactivating mutations of the gene *PHEX*, encoding a member of the neutral endopeptidase family of proteins, are responsible for XLH (refs 6,7). ADHR (MIM 193100) is characterized by low serum phosphorus concentrations, rickets, osteomalacia, lower extremity deformities, short stature, bone pain and dental abscesses[4,5]. Here we describe a positional cloning approach used to identify the ADHR gene which included the annotation of 37 genes within 4 Mb of genomic sequence. We identified missense mutations in a gene encoding a new member of the fibroblast growth factor (FGF) family, *FGF23*. These mutations in patients with ADHR represent the first mutations found in a human FGF gene.

(ref. 8). The two-point lod score for marker *D12S1624* was 7.68. A second, smaller ADHR kindred, family 1478, had a lod score of 1.1 at *D12S1624*. Assuming that the disease locus in this family was linked to the same interval, we screened for single recombination events in these two families. Distal and proximal recombinations in families 1406 and 1478, respectively, provisionally mapped the disease locus to the 1.5-Mb region between the markers *D12S1685* and *D12S1594*.

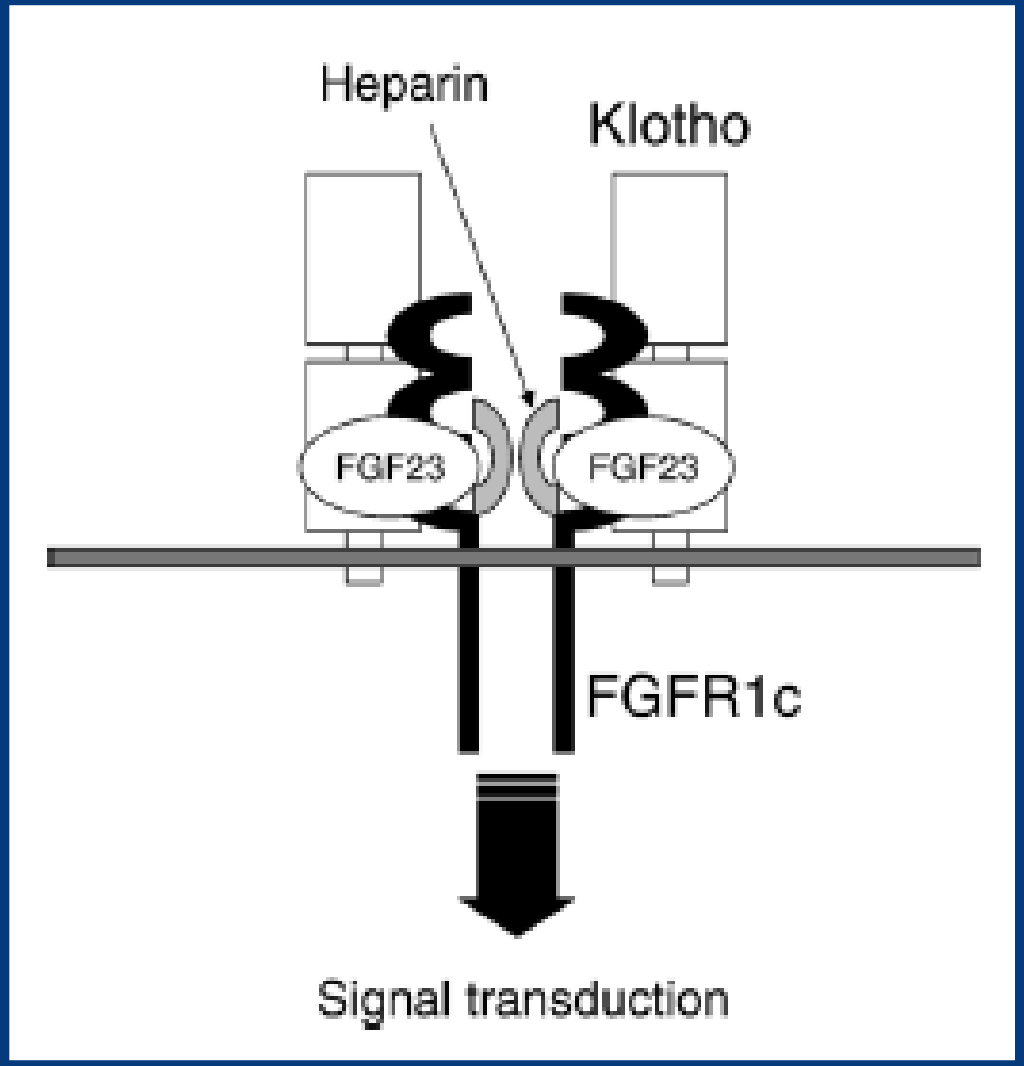
Genomic sequences from chromosome 12p13 are available from the public human genome effort. Analysis of finished and unfinished sequences between *D12S1685* and *D12S1623* revealed 37 genes within this region, 13 of which are new genes (available with the transcription map at http://www.pedgen.med.uni-muenchen.de/chr12/index.html). The complete coding sequences of the new genes were obtained by RT–PCR, RACE and/or sequencing of IMAGE clones.

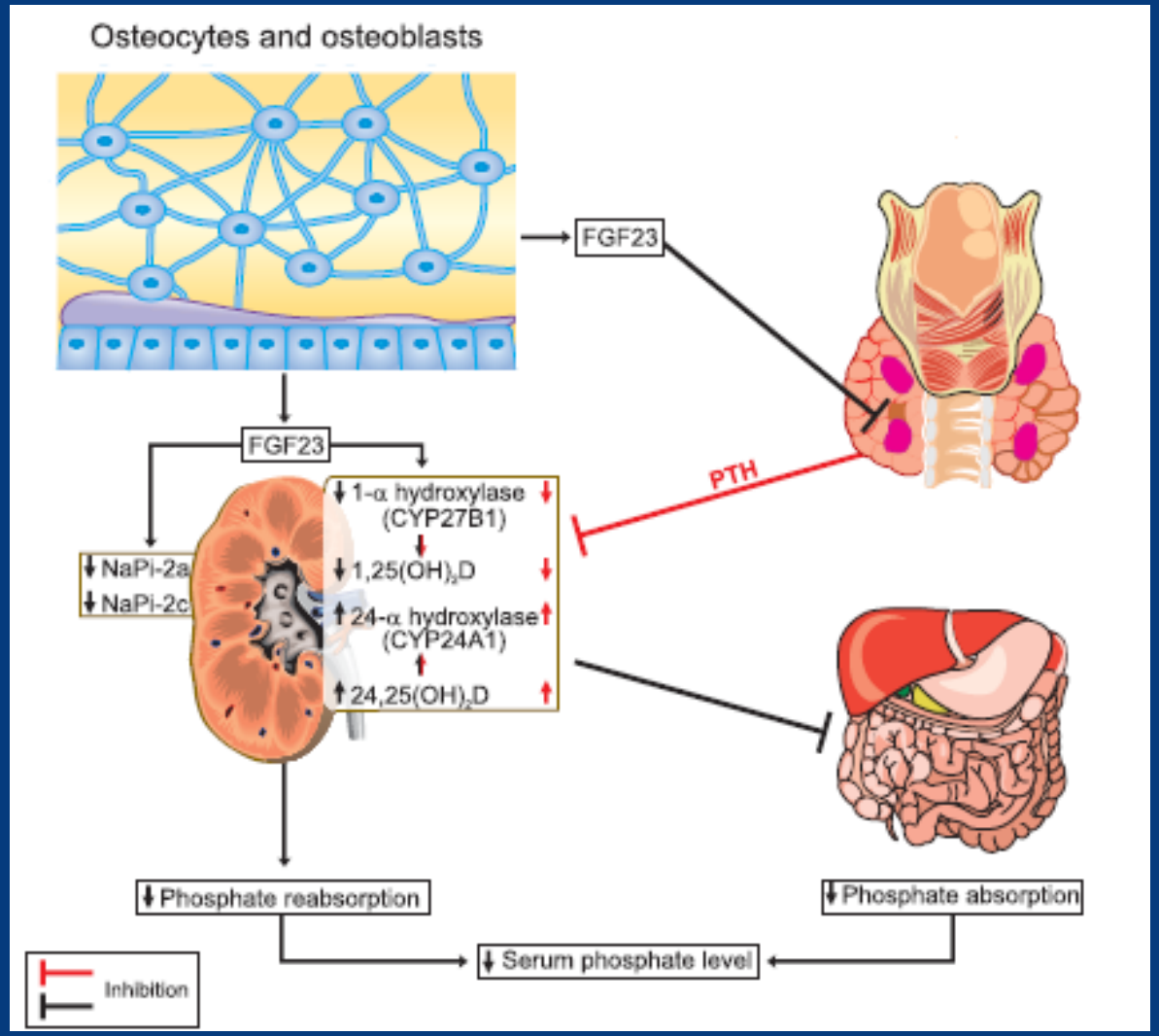
For mutation screening, we used DNA from index patients of 4 families that had male-to-male transmission and clinical features compatible with ADHR, including the families 1406 and 1478, as well as DNA from 18 patients with hypophosphataemic rickets that were negative for *PHEX* mutations. We also analysed



Nature Rev Nephrol 2019

Δράσεις FGF23





Minisola S, et al. ER 2023

Υποφωσφοραιμία

mmol/L to mg divide by 0.3229

	Serum phosphate (mg/dL)	Serum phosphate (mmol/L)
0–5 days	4·8–8·2	1·5–2·6
1–3 years	3·8–6·5	1·2–2·1
4–11 years	3·7–5·6	1·2–1·8
12–15 years	2·9–5·4	0·9–1·7
16–19 years	2·7–4·7	0·9–1·5
≥20 years	2·5–4·5	0·8–1·4

Table 1: **Normal age-dependent values of serum phosphate**

Βαρύτητα υποφωσφοραιμίας

- Mild (0,6–0,8 mmol/L; 1,8–2,5 mg/dL)
- Moderate (0,4–0,5 mmol/L; 1,0–1,7 mg/dL)
- Severe (P <0,3 mmol/L; 0,9 mg/dL).

Υποφωσφοραιμία

- Χρονιότητα: Οξεία-Χρόνια
- Παθοφυσιολογία
  - Μειωμένη Εντερική Απορρόφηση
  - Αυξημένη Είσοδος P ενδοκυττάρια ή εναπόθεση P στους ιστούς
  - Αυξημένη Νεφρική Απώλεια
    - PTHR-1 dependent
    - FGF23 dependent
    - FGF23 independent

Υποφωσφοραιμία

1. Μειωμένη εντερική απορρόφηση φωσφόρου

- Αλκοολισμός
- Ένδεια βιταμίνης D, VDDR 1-3
- Σύνδρομα δυσαπορρόφησης

2. Αυξημένη είσοδος φωσφόρου εντός των κυττάρων ή εναπόθεση P στους ιστούς

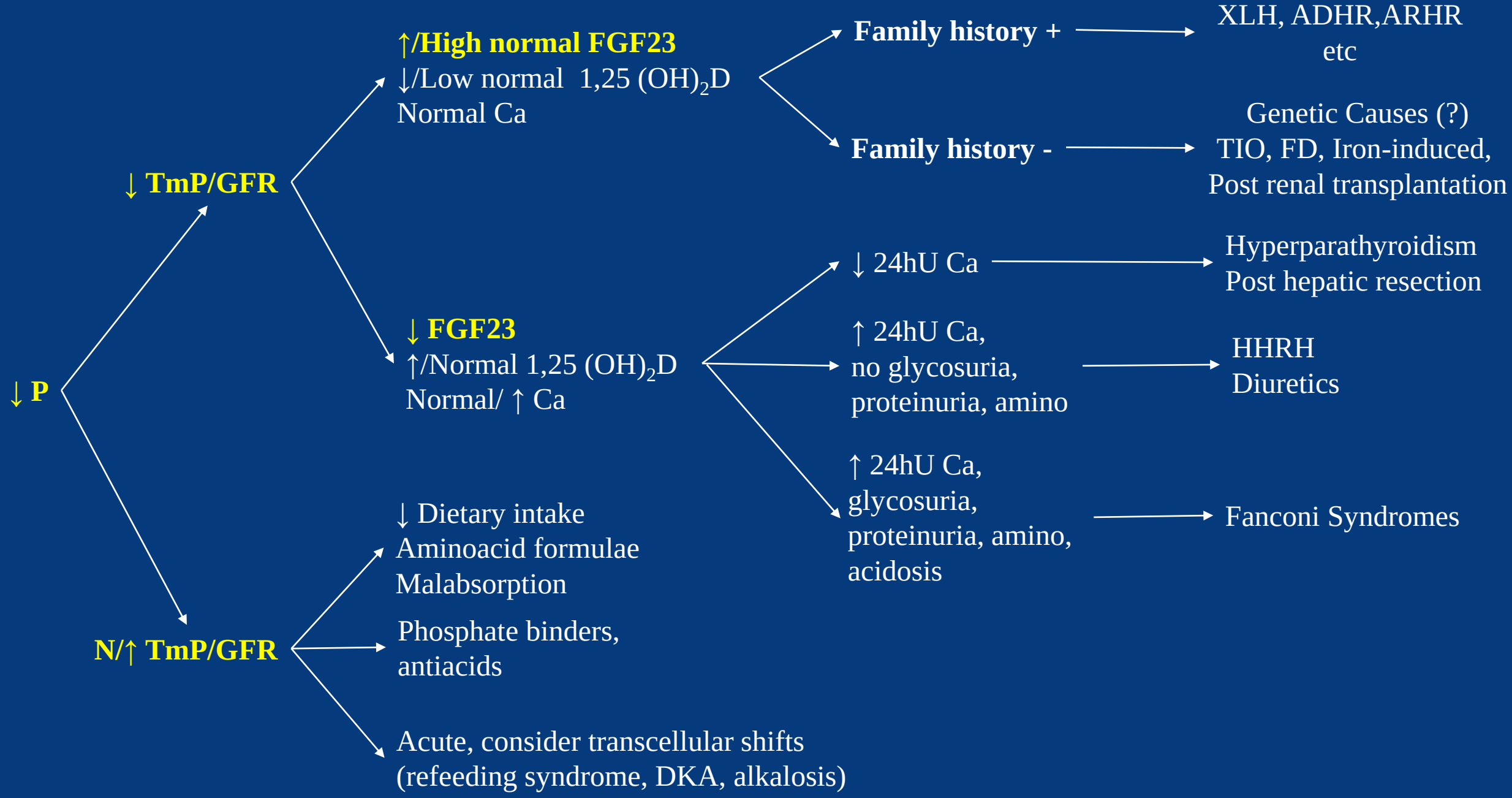
- Χορήγηση ινσουλίνης για την διόρθωση της κετοξέωσης
- Παρεντερική σίτιση
- Απόσυρση από το αλκοόλ
- Αναπνευστική αλκάλωση
- Δηλητηρίαση με σαλικυλικά
- Hungry bone syndrome
- Θεραπεία κακοήθους αναιμίας
- Σηψαιμία από gram αρνητικά μικρόβια
- Οξεία λευχαιμία (λόγω ταχέως πολλαπλασιαζόμενων κυττάρων)
- Μετεμφραγματικοί και πολυτραυματίες
- Εγκαύματα

3. Αυξημένη νεφρική απώλεια φωσφόρου

- PTH/PTHrP dependent
  - Πρωτοπαθής υπερπαραθυρεοειδισμός
  - Δευτεροπαθής υπερπαραθυρεοειδισμός
  - Χονδροδυσπλασία του Jansen
  - Κακοήθειες (μέσω αύξησης του PTHrp, συνηθέστερα ο καρκίνος του μαστού)

Υποφωσφοραιμία- Νεφρική Απώλεια Φωσφόρου

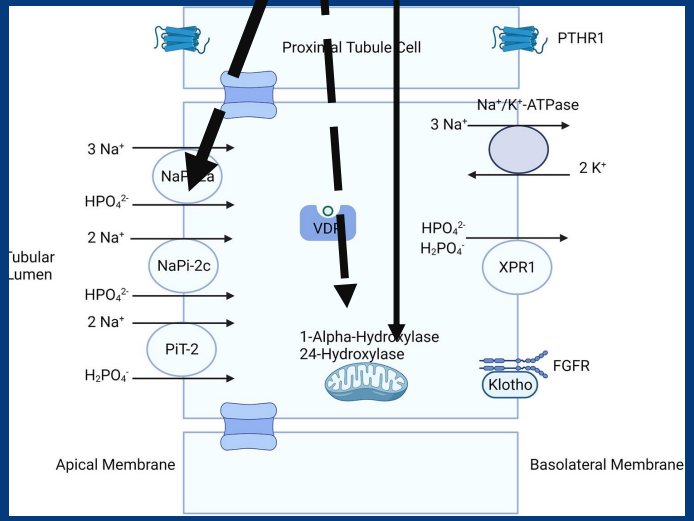
- **FGF23 dependent**
  - Επίκτητες
    - Ογκογενής Οστεομαλακία
    - Ενδοφλέβια χορήγηση σιδήρου
    - Μετά από μεταμόσχευση νεφρού
  - Κληρονομικές
    - XLHR
    - ADHR
    - Υποφωσφοραιμική ραχίτιδα με υπερπαραθυρεοειδισμό
    - ARHR 1,2,3
    - Πολυοοστοτική ινώδης δυσπλασία
    - Cutaneous-Skeletal hypophosphatemia syndrome
- **FGF23 independent**
  - Σωληναριακές βλάβες
    - Phosphate-specific tubulopathies
      - Κληρονομική υποφωσφοραιμική ραχίτιδα με ασβεστιουρία (HHRH-SLC34A3)
      - Υποφωσφοραιμία με νεφρασβέστωση (SLC34A1)
      - SLC9A3R1 (NHERF1)
    - Σύνδρομο Fanconi
      - Επίκτητο
      - Κληρονομικό
  - Φάρμακα
    - Ακεταζολαμίδη
    - Διουρητικά
    - Στεροειδή
    - Αντικαταβολικά (BSP, Dmab, Estrogen)
    - NSAIDs



Ackah SA, Imel EA. JCEM 2023

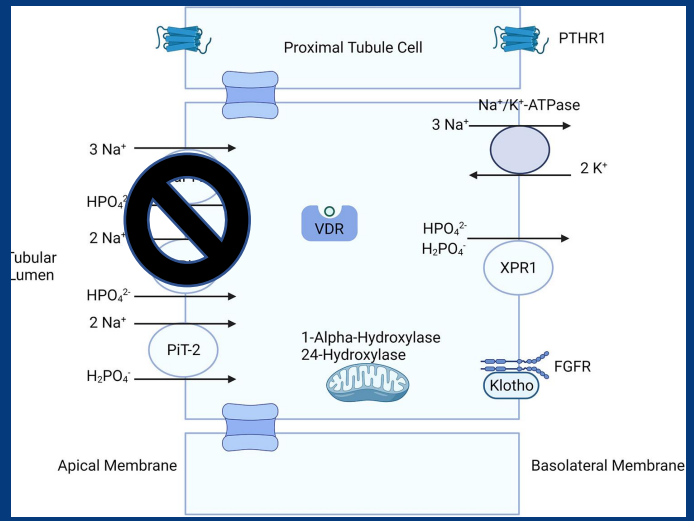
Υποφωσφοραιμία- Νεφρική Απώλεια Φωσφόρου

↑↑ FGF23



↑ νεφρικής αποβολής φωσφόρου
↓ TmP/GFR
↓ P
↓ 1,25 $(OH)_2D$

FGF23 independent e.g. Fanconi



↑ νεφρικής αποβολής φωσφόρου
↓ TmP/GFR
↓ P

↓ FGF23
↑ CYP27B1, ↓ CYP24A1
-/↑1,25 $(OH)_2D$
↑ Ca, ↓ PTH, ↑ 24UCa

X-Linked hypophoshatemic Rickets

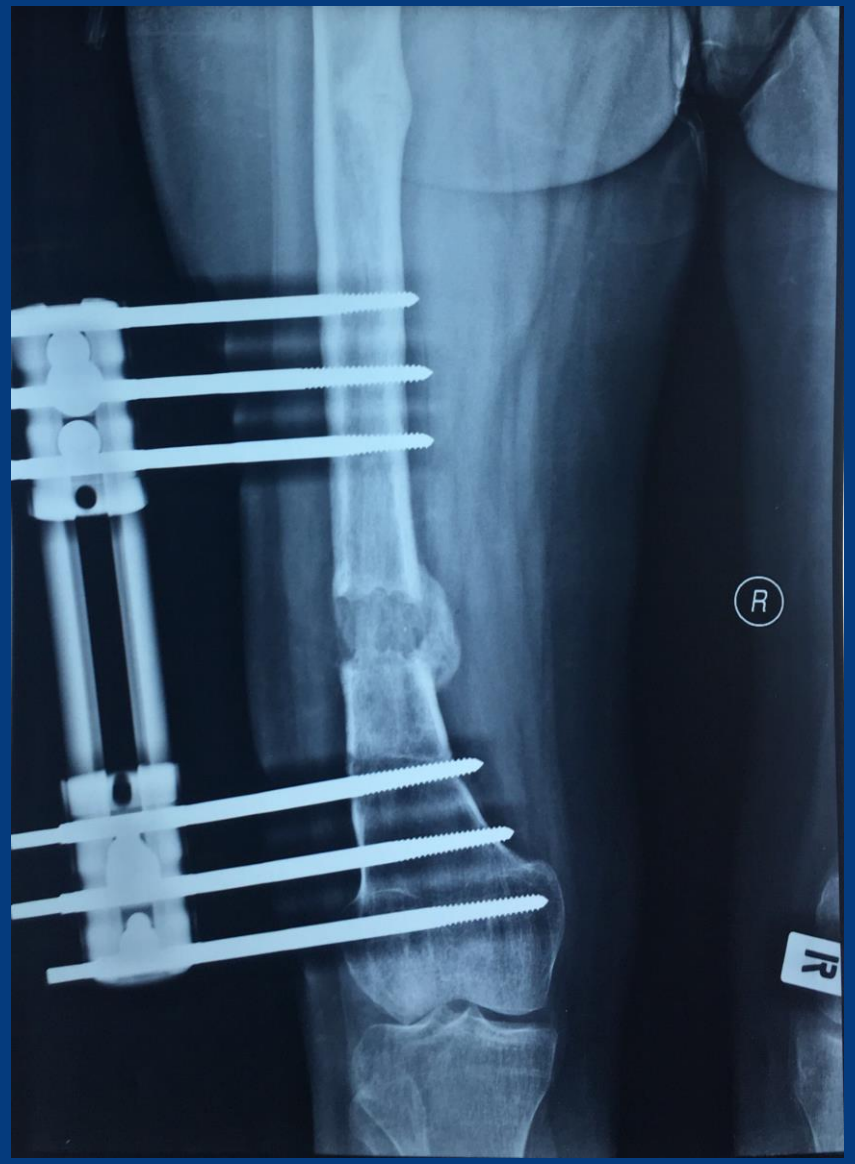
- Επίπτωση: 3,9/ 100000 live births, Επιπολασμός: 1,7/100000 (παιδιά)- 4,8/100000 (σύνολο)
- X- linked επικρατούσα διαταραχή συνεπεία μεταλλάξεων στο *PHEX* (located at Xp22.1)
- 20-30% είναι σποραδικές
- Η βαρύτητα δεν τροποποιείται με τις γενεές
- Η νόσος παραμένει σε βαρύτητα και μετά την ενηλικίωση
- Η βαρύτητα ποικίλη ακόμα και σε άτομα τις ίδιας οικογένειας
- Όχι σαφής συσχέτιση φαινότυπου-γονότυπου

Κλινική Εικόνα

- Κοντό ανάστημα
- Ραχίτιδα, με παραμορφώσεις στα κάτω άκρα (2/3 των ασθενών διορθωτικές επεμβάσεις)
- Οστεομαλακία/κατάγματα ανεπάρκειας (50%)
- Οστικά άλγη
- Ενθεσοπάθεια, οστεοαρθρίτιδα
- Οδοντικά αποστήματα (50%)
- Ανωμαλίες του κρανίου, σπονδυλική στένωση, διαταραχές ακοής
- Αρτηριακή υπέρταση, LVH
- Νεφρασβέστωση (50-70%)

Παρακλινικά ευρήματα

- Υποφωσφοραιμία
- Φωσφορουρία, low UCa
- Μειωμένο TMP/GFR (maximal tubular reabsorption of phosphate per GFR) [φτ=2,5-4,2 mg/dl]
- Ca: normal/low
- iPTH: normal/high
- 25 (OH)D: φυσιολογικά
- 1,25 $(OH)_2$ D: ανάρμοστα φυσιολογικά
- FGF-23 : συνήθως αυξημένος
- Γενετικός έλεγχος: θετικός στο 70-90%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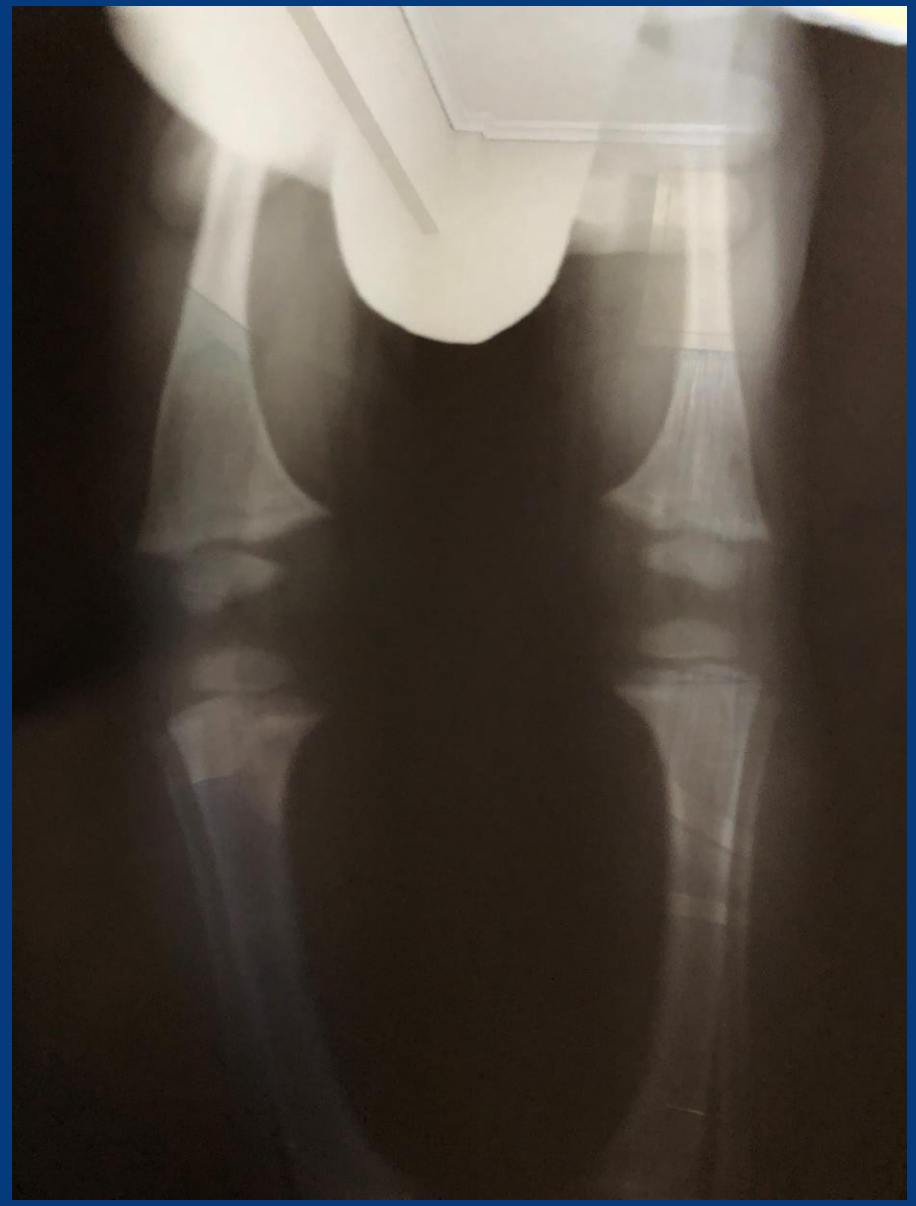


Interdisciplinary management of FGF23-related phosphate wasting syndromes: a Consensus Statement on the evaluation, diagnosis and care of patients with X-linked hypophosphataemia

Nature Reviews Endocrinology 2022

Conventional treatment in children: recommendations.

- Vitamin D analogues and phosphate supplements can be offered to all children with XLH, as soon as the diagnosis is established.
- Starting doses of elemental phosphate range from 20 to 60 mg/kg body weight per day (0.7–2.0 mmol/kg)[2] in four to six divided doses, according to the severity of the disease.
- Calcitriol should be given at a starting dose of 20–30 ng/kg body weight per day, in one or two doses, or alfacalcidol once daily at an initial dose of 30–50 ng/kg per day.

Conventional treatment in adults: recommendations.

- Treatment in adults should include: vitamin D analogues (alfacalcidol 0–1.5 µg per day, once per day, or calcitriol 0–1.0 µg per day, in one or two doses) alone or with phosphate supplements (ideally smaller doses (than in children), which are evenly distributed across the day, 0–2,000 mg per day).
- Management of bone pain might be required in adults with XLH owing to osteomalacia, fractures or pseudofractures.
- In adults with XLH, clinicians should evaluate the need for orthopaedic surgery or the presence of dental complications.
- We suggest considering treatment with vitamin D analogues and phosphate supplements during pregnancy and breastfeeding. No data, to our knowledge, are available regarding the effect of therapy in postmenopausal women. Consistent evidence is still missing for treating enthesopathies.
- We do not recommend treatment of asymptomatic adult patients, unless they develop pseudofractures, even without symptoms.

Burosumab- Indications

Nature Reviews Endocrinology 2022

Burosumab treatment in children: recommendations.

- Consider burosumab treatment as first-line therapy in children with XLH aged 1 year or older (6 months in some countries, such as the USA), and in adolescents with radiographic evidence of severe bone disease.
- In children with mild disease, a trial of conventional therapy is suggested rather than considering burosumab as a first-line therapy.
- Once started, treatment with burosumab should be continued until the closure of the growth plate. A multidisciplinary evaluation should be conducted with the adult team to consider the follow-up of burosumab through adulthood.

Burosumab treatment in adults: recommendations.

- Burosumab could be suggested as a second-line therapy in adults with XLH with overt osteomalacia, with pseudofractures that are not responding to conventional treatment or in patients intolerant to conventional treatment.

Children: The starting dose of burosumab is 0.8 mg/kg/2 weeks sbc
(maximum dose 2 mg/kg per 14 days or 90 mg per 14 days).
Adults: 1 mg/kg/4 wks

Ογκογενής Οστεομαλακία

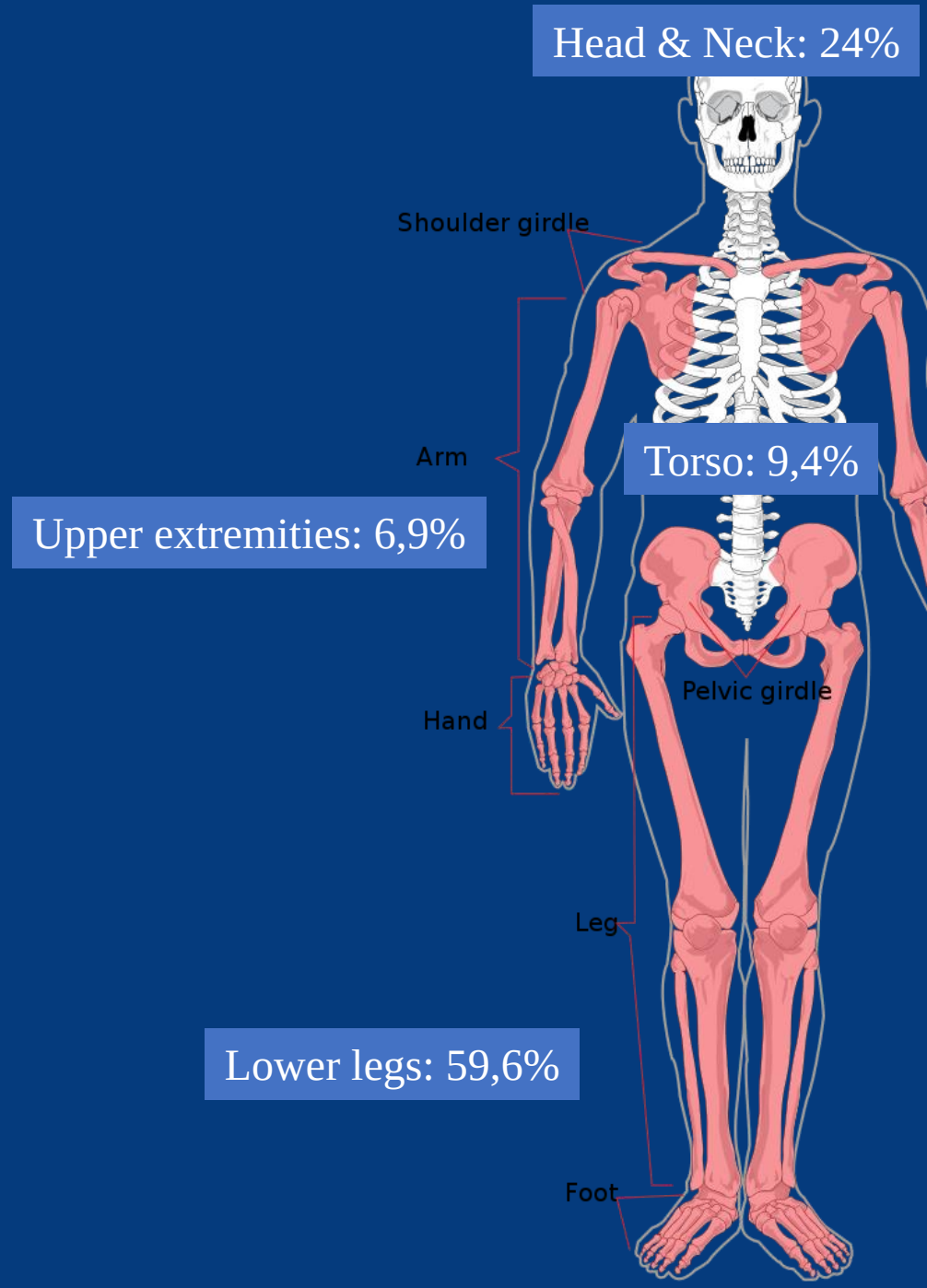
- Πρώτη αναφορά από τον McCance 1947
- Συσχέτιση με μεσεγχυματικούς όγκους από τον Prader, 1959
- Συσχέτιση με «φωσφατονίνες» το 1994 από τον Cai.
- Ετήσια επίπτωση FGF23- υποφωσφοραιμίας (Japan): **0,04/100000 persons/year**
- Denmark: prevalence : **0.70 per 100,000 persons for the total population and only 0.43 per 100,000 persons in adults**, [2018: 9 new cases] (Abrahamsen B, CTI 2021)
- Συνήθως κατά την 4η-5η δεκαετία της ζωής
- Ταξινόμηση Oncogenic Osteomalacia (OOM) (CTI 2020)
  - Phosphaturic Mesenchymal Tumor (PMT)- Tumor Induced Osteomalacia (TIO)
  - Cancer – Associated osteomalacia (CAO)

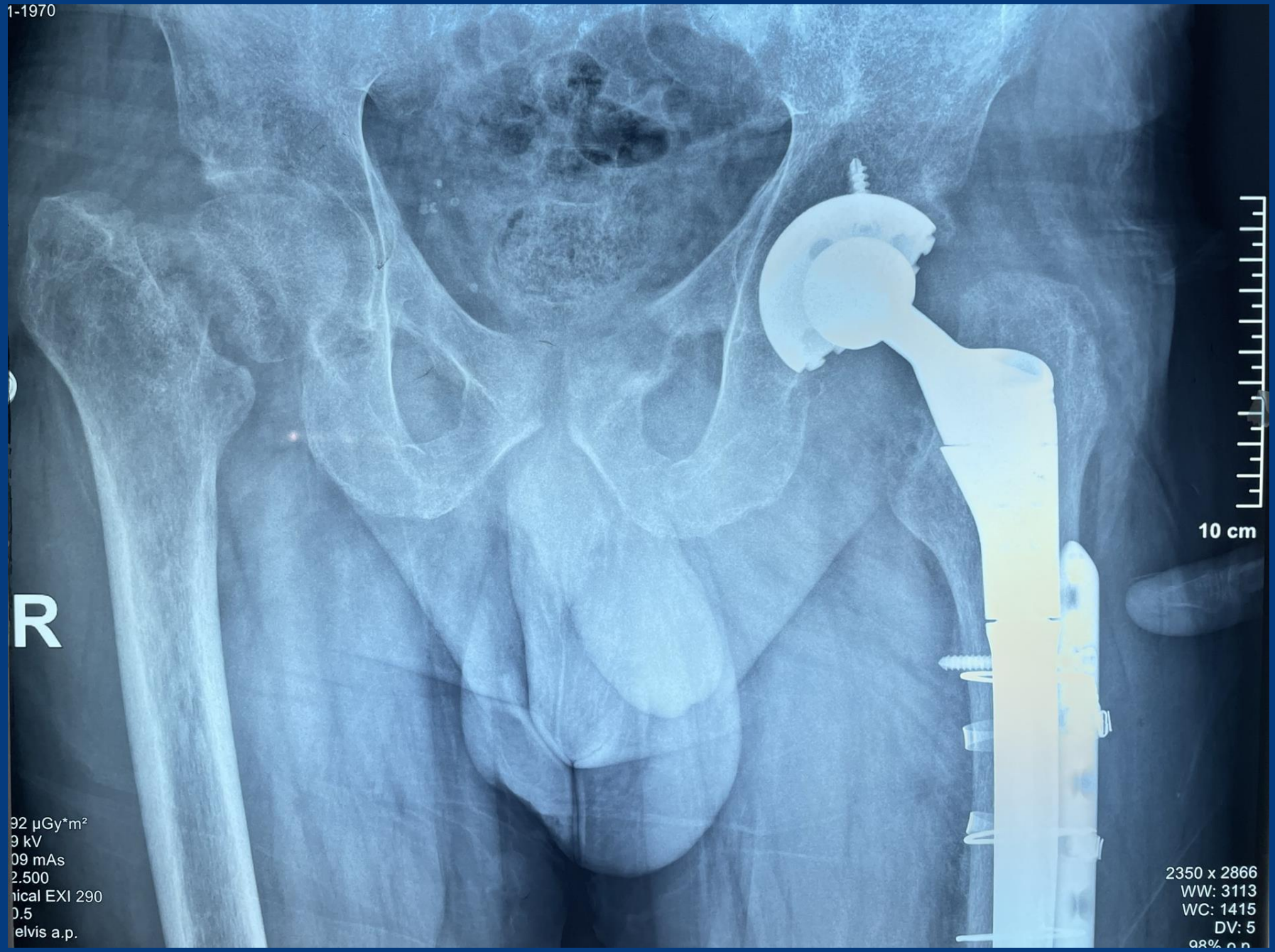
Όγκοι

- Phosphaturic Mesenchymal Tumor (PMT) – mixed connective tissue variant (TIO)
  - Admixture of spindle cells, osteoclasts-like giant cells, microcysts, prominent blood vessels, cartilage-like matrix, and grungy calcification
- Cancer – Associated osteomalacia (CAO) - (συμπαγείς όγκους-αιματολογικές κακοήθειες)
- Βιολογική συμπεριφορά
  - Κατά κανόνα καλοήθεις
  - 2% πολυεστιακούς καλοήθεις όγκους
  - < 5% κακοήθεις

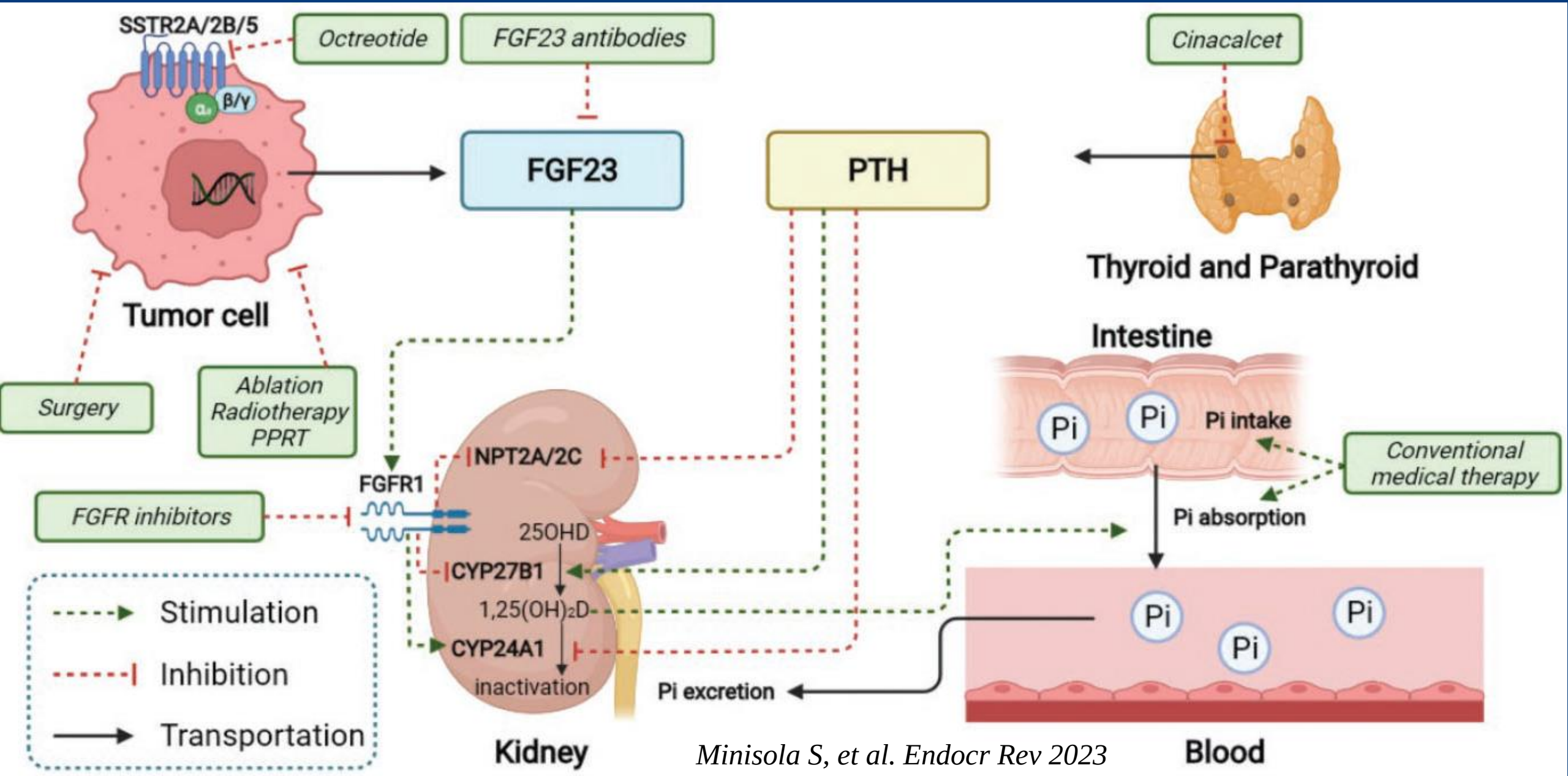
Εντόπιση

- Μαλακοί Ιστοί : άκρα
- Οστά : περιφερικό σκελετό, κρανίο, παραρρίνιους κόλπους
- Functional Imaging
  - Whole-body 68GaDOTATATE PET-CT
  - (HYNIC)-octreotide (^{99m}Tc) SPECT-CT
  - Octreoscan (^{111}In)
  - 18F-FDG PET-CT
- Imaging
  - MRI
  - CT
- Venous sampling
- FNA: ??



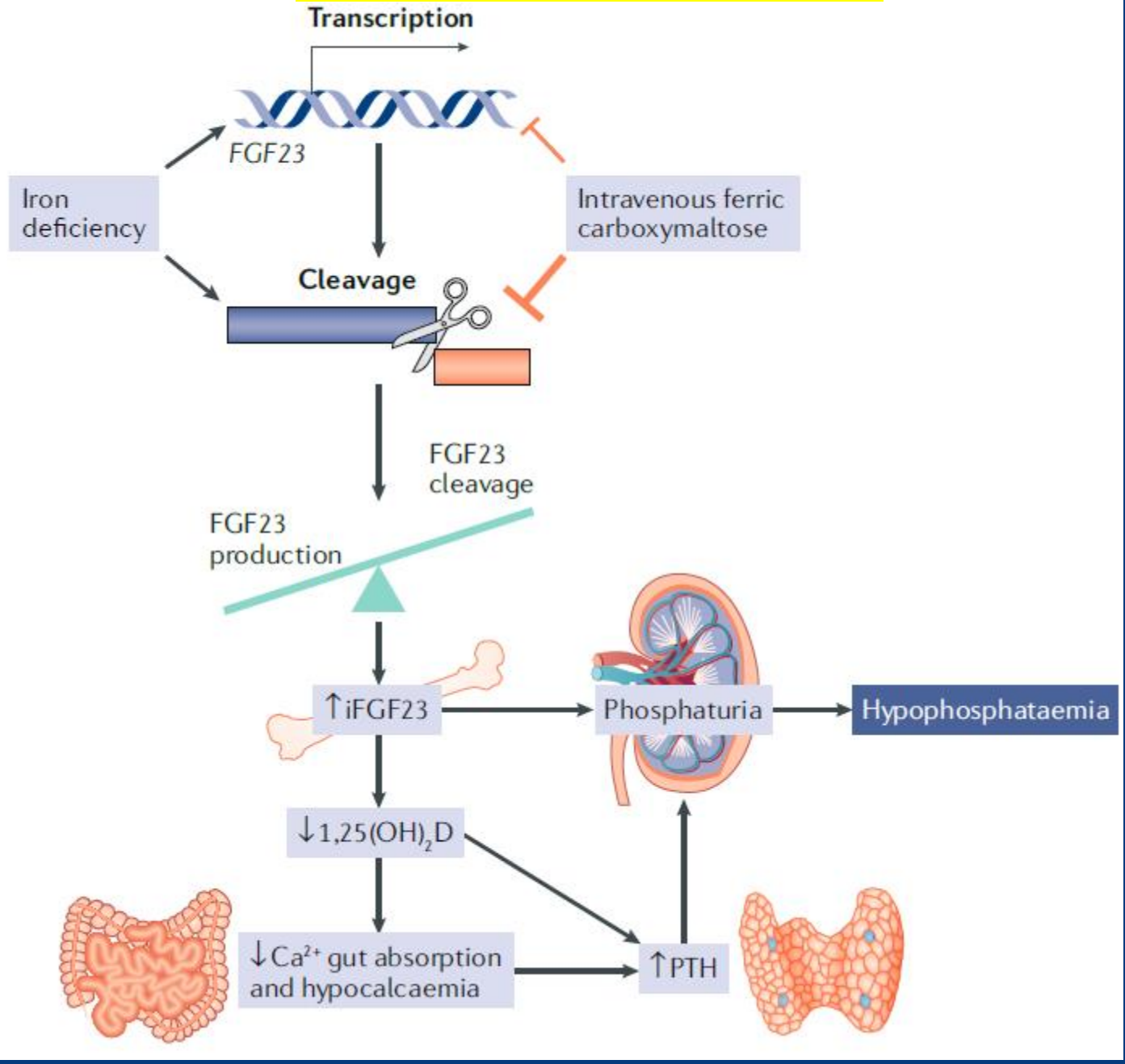

1-1970
R
10 cm
92 µGy*m²
9 kV
09 mAs
2.500
nical EXI 290
0.5
elvis a.p.
2350 x 2866
WW: 3113
WC: 1415
DV: 5

Mechanism of actions for the existing and potential novel therapies.



Minisola S, et al. Endocr Rev 2023

Iron Induced Hypophosphatemia



Clinical Research Article

Risk Factors for and Effects of Persistent and Severe Hypophosphatemia Following Ferric Carboxymaltose

Benedikt Schaefer,[1] Heinz Zoller,[1] and Myles Wolf[2]

JCEM 2022;107: 1009–1019

no hypophosphatemia (serum phosphate ≥ 2.0 mg/dL at all visits),
moderate hypophosphatemia (serum phosphate 1.0 to < 2.0 mg/dL at any post-baseline visit),
severe hypophosphatemia (serum phosphate ≤ 1.0 mg/dL at any post-baseline visit;

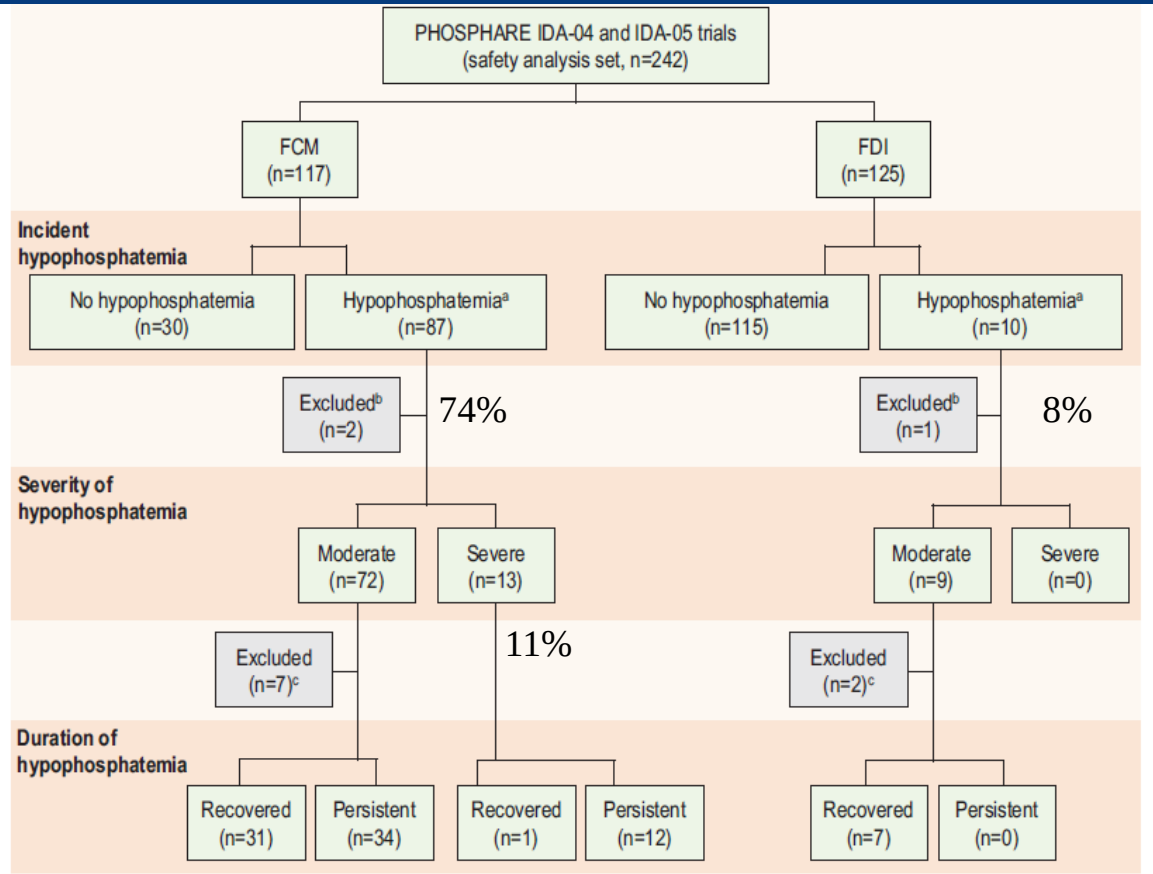


Figure 1. Patient flow according to study drug, hypophosphatemia severity, and hypophosphatemia duration. Abbreviations: FCM, ferric carboxymaltose; FDI, ferric derisomaltose. [a]For patients with no post-baseline measurements, serum phosphate level was imputed as < 2.0 mg/dL (as in the primary clinical trial analysis). [b]Patients with no post-baseline serum phosphate measurements. [c]Patients who could not be categorized according to the definitions of "recovered" and "persistent," due to low phosphate only on day 21 and/or day 35.

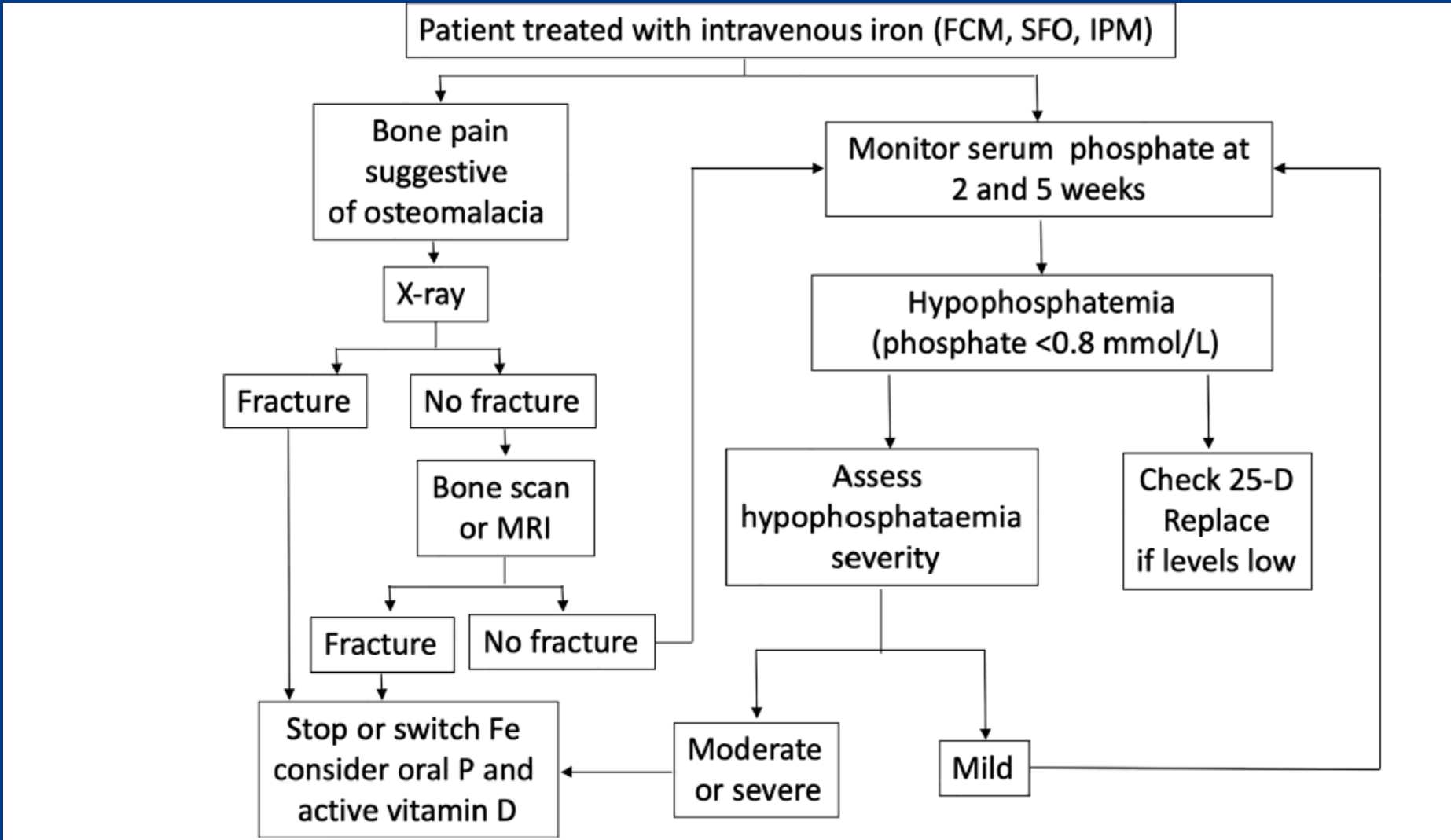


Fig. 2. Proposed algorithm for diagnosis and management of osteomalacia associated with repeated iron infusions.

ferric carboxymaltose (FCM), saccharated ferric oxide (SFO), iron polymaltose (IPM).

Journal of Bone and Mineral Research, Vol. 37, No. 6, June 2022, pp 1188–1199

Cases

Ογκογενής Οστεομαλακία

Άνδρας 50 ετών

	9/2/2020
Κρεατινίνη (mg/dl)	0,9
Ασβέστιο (mg/dl)	8,8
Φώσφορος (mg/dl)	1,4
Μαγνήσιο (mg/dl)	1,9
ALP IU/L (40-150)	260
Αλβουμίνη (gr/dl)	4,5
PTH (pg/ml)	99
25 (	
1,25 D (pg/ml)	< 8
Ca U 24h (mg)	101
P U 24h (mg)	670
V U 24h	700
Creat U 24h (mg)	1510
TMP/GFR mg/dl	1.0159

FGF 23: 900 pg/ml

β/π Σ. Fanconi

Γυναίκα 48 ετών

Κρεατινίνη (mg/dl)	1,3	1,27
Ασβέστιο (mg/dl)	8,7	9,1
Φώσφορος (mg/dl)	2	2,1
Μαγνήσιο (mg/dl)	2,2	2,2
ALP IU/L (40-150)	329	258
UA (mg/dl)	1,7	2,4
Αλβουμίνη (gr/dl)	4,6	4,7
PTH		
25 (OH) D (ng/ml)	37,1	31
1,25 D (pg/ml)		26,1
Ca U 24h (mg)		59
P U 24h (mg)		488
V U 24h		1600
Creat U 24h (mg)		672
TMP/GFR mg/dl (2,4-4,2)		1,7778

FGF 23: < 50 RU/ml

Μεικτή Υποφωσφοραιμία από χορήγηση IV σίδηρο και δυσαπορρόφηση

Άνδρας 31 ετών

Κρεατινίνη (mg/dl)	0,59
Ασβέστιο (mg/dl)	8,0
Φώσφορος (mg/dl)	1,2
Μαγνήσιο (mg/dl)	1,78
ALP IU/L (40-150)	71
Αλβουμίνη (gr/dl)	3,5
PTH (pg/ml)	82,9
25 (	
1,25 D (pg/ml)	19
Ca U 24h (mg)	28
P U 24h (mg)	540
V U 24h	1400
Creat U 24h (mg)	881
TMP/GFR mg/dl (2,4-4,2)	0,8383

FGF 23: 96 pg/ml