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CONGRESSO NAZIONALE GISMO

MALATTIE MUSCOLO-SCHELETRICHE
TERAPIA INTEGRATA, PERSONALIZZATA E QUALITÀ DI VITA
ROMA 6 - 7 ottobre 2023

GISMO

Gruppo Italiano Studio
malattie Metabolismo Osseo

- Osteoporosi
- Malattie Muscolo-Scheletriche
- Malattie Metaboliche
- Dolore
- Nutrizione



Dott. Luciano Colangelo



Sapienza Università di Roma



*Le ipofosforemie: dalla
fisiopatologia alla terapia*

Omeostasi del fosfato BONE-KIDNEY-GUT NETWORK

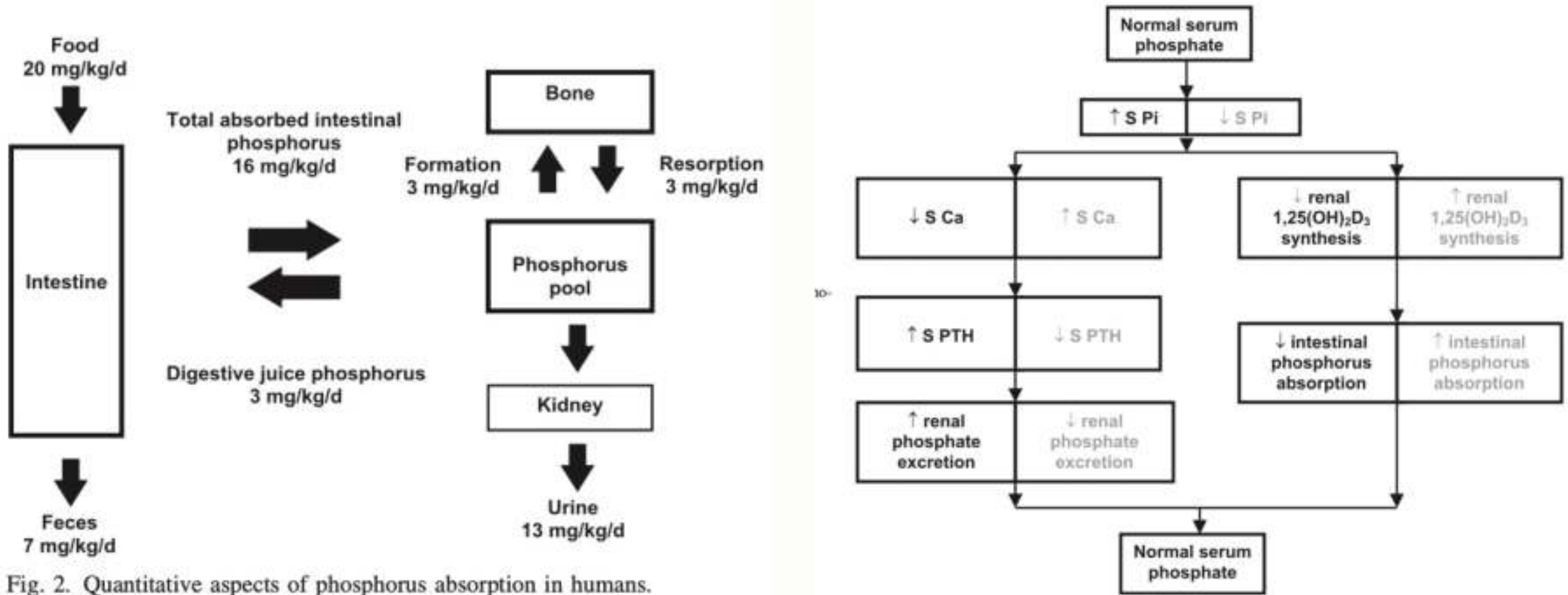


Fig. 2. Quantitative aspects of phosphorus absorption in humans.

Prevalenza Ipofosfatemia

- Hospitalised patients (2.2-3.1%)
- Sepsis (65-80%)
- 1088 patients enrolled in oncology clinical trials showed an unexpected 32% prevalence of hypophosphatemia
- Intensive Care Unit (29-34%)

Koljonen et al. JCEM, 2021;106(10):2865-2875

Florenzano P. et al Lancet Diabetes Endocrinol 2020

Impact of hypophosphatemia on outcome of patients in intensive care unit: a retrospective cohort study



Lichun Wang, Chaoxing Xiao, Lei Chen, Xiaofei Zhang and Qiuye Kou*

Abstract

Background: Hypophosphatemia generally occurs in Intensive Care Units (ICUs), but its impact is often ignored. The aim of this study was to investigate whether hypophosphatemia can be a risk factor for ICU 28-day mortality.

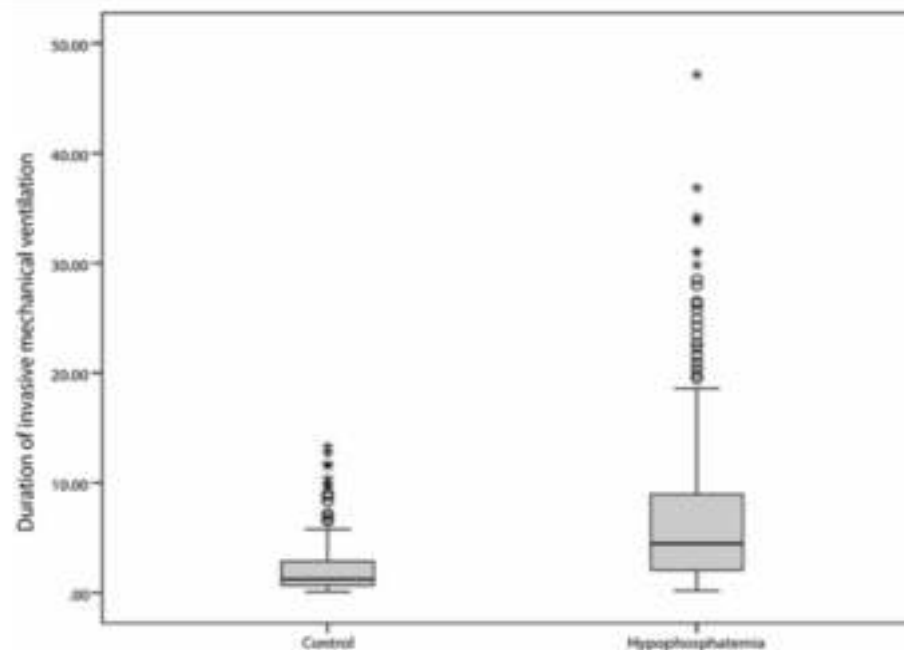


Fig. 2 Duration of invasive mechanical ventilation

Approccio al paziente con ipofosfatemia e diagnosi differenziale

Escludere pseudo-ipofosfatemie:

- Fattori pre-analitici
- Equilibrio acido-base
- Disordini mielo-linfoproliferativi
-

	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

Normal age-dependent values of serum phosphate

Rule out condizioni cliniche acute:

- Alcalosi respiratoria acuta
- Chetoacidosi diabetica/sindrome iperglicemica iperosmolare
- Refeeding syndrome

Refeeding syndrome as described in 1507 by Antonio Benivieni in Florence

Natale G. De Santo¹, Carmela Bisaccia², Malcolm E. Phillips³ and Luca S. De Santo⁴

adeo noxia atque pernitiōsa est nimia satietas, quam multa praecessit inedia

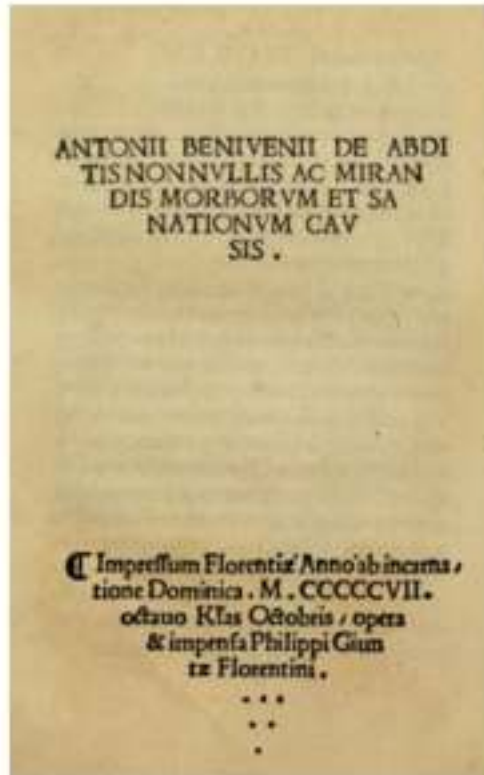


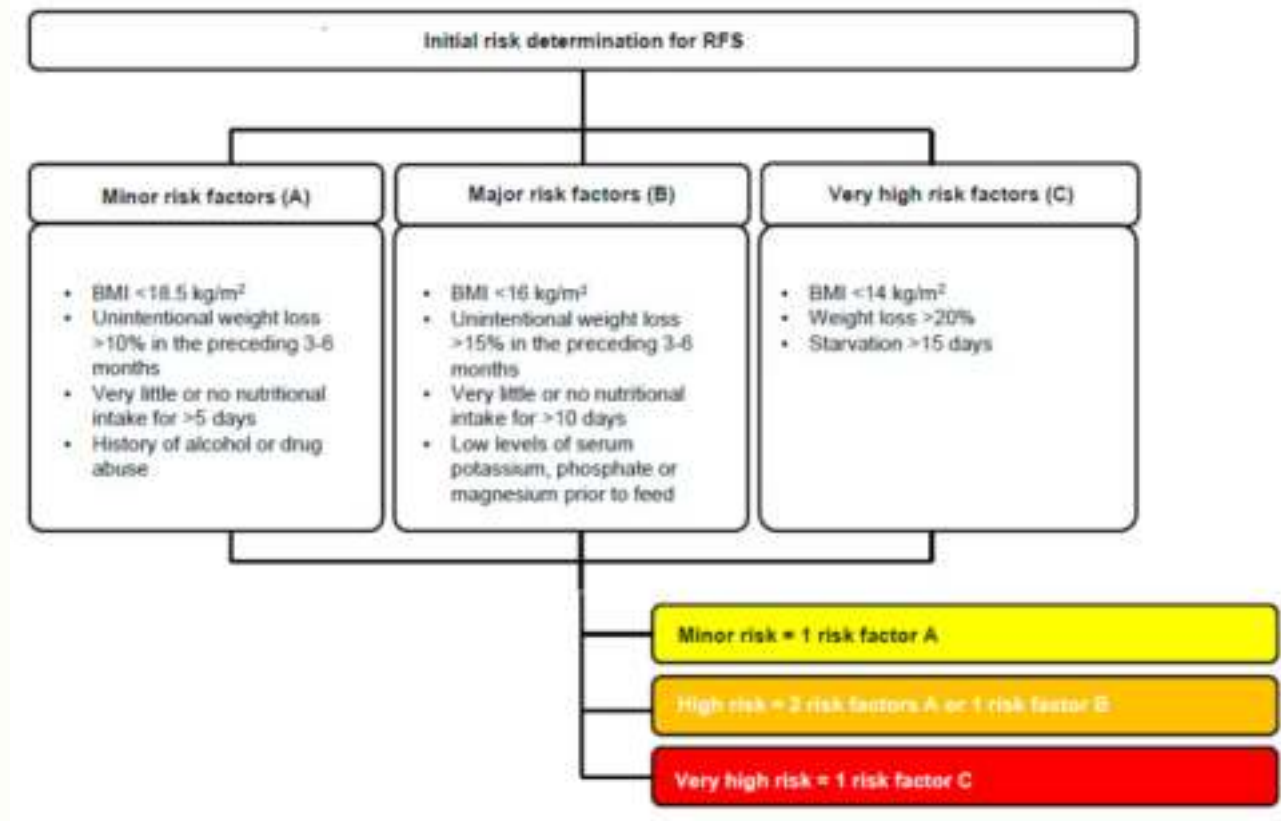
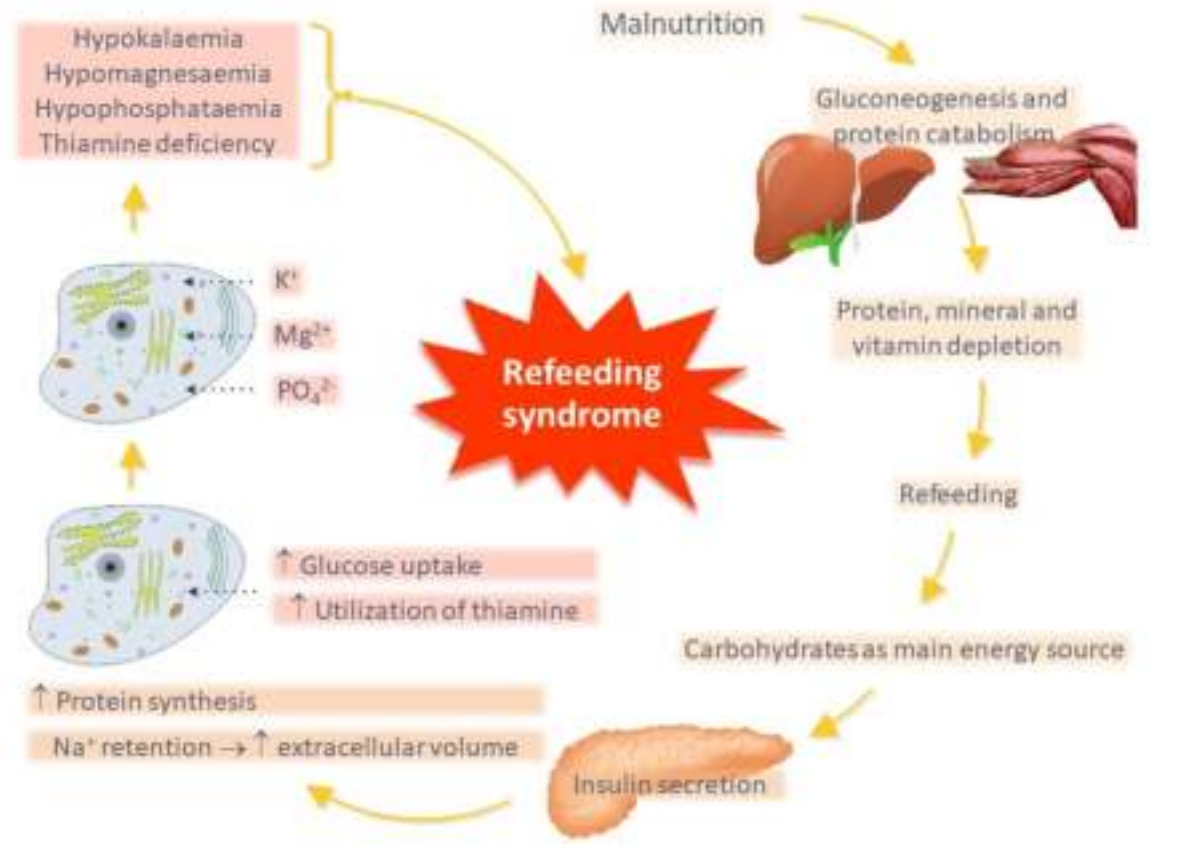
FIGURE 1: Antonio Benivieni (1443–1502). Reprinted with permission from Ref. [36].

is richer in data than all compilation books written in the century before his' [30].

For Sprengel (1766–1835), Benivieni was with Antonio Benedetti (c1450–1512) one of the two scientists who, in that century, did not copy Arab authors, but produced original find-

"In the year 1496 extensive famine affected nearly the whole of Italy, so that many died on the public roads and city streets. Many also, through bad and injurious foods, were attacked by various disorders. I noticed too that very many of those who had, after prolonged fasting, obtained more abundant food, enjoyed their fuller nourishment for a few days and then died (*dum pleniori utunturs victu, paucis diebus vitam finisse*), so harmful and dangerous is satiety preceded by a long period of abstinence (*adeo noxia atque pernitiōsa est nimia satietas, quam multa praecessit inedia*). I also saw women who in this way did harm to the children at their breast, and so brought death upon their children and themselves (*et se et illos ad mortem deducerent*). But

Fisiopatologia della refeeding syndrome



1. DECREASED INTESTINAL ABSORPTION

- Decrease in phosphate intake
- Phosphate binding antacids
- Vitamin-D deficiency/resistance
- Malabsorption

2. REDISTRIBUTION HYPOPHOSPHATEMIA

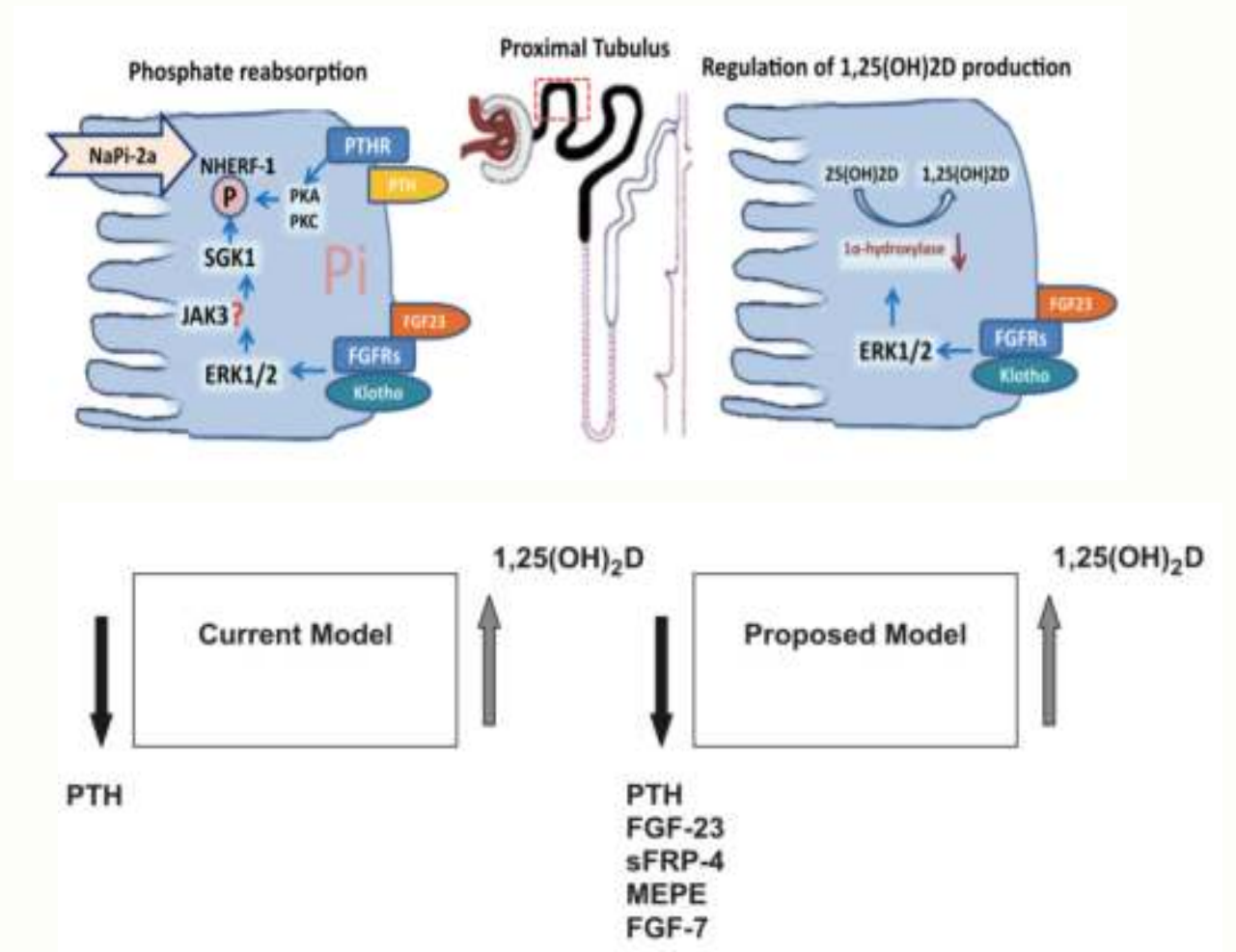
- Respiratory alkalosis
- Refeeding hypophosphatemia
- Hormonal-induced
- Rapid cell proliferation

3. RENAL HYPOPHOSPHATEMIA

- Primary tubular damage
 - Hereditary
 - Acquired
- Circulating factors
 - Hyperparathyroidism
 - PTHrp
 - Phosphatonins
 - Tumor-induced osteomalacia
 - ADHR
 - XLH
- Volume expansion
- Diuretics
- Liver resection

4. MULTIPLE FACTORS

- Diabetic ketoacidosis
- Alcoholism
-



INQUADRAMENTO DELL'IPOFOSFOREMIA

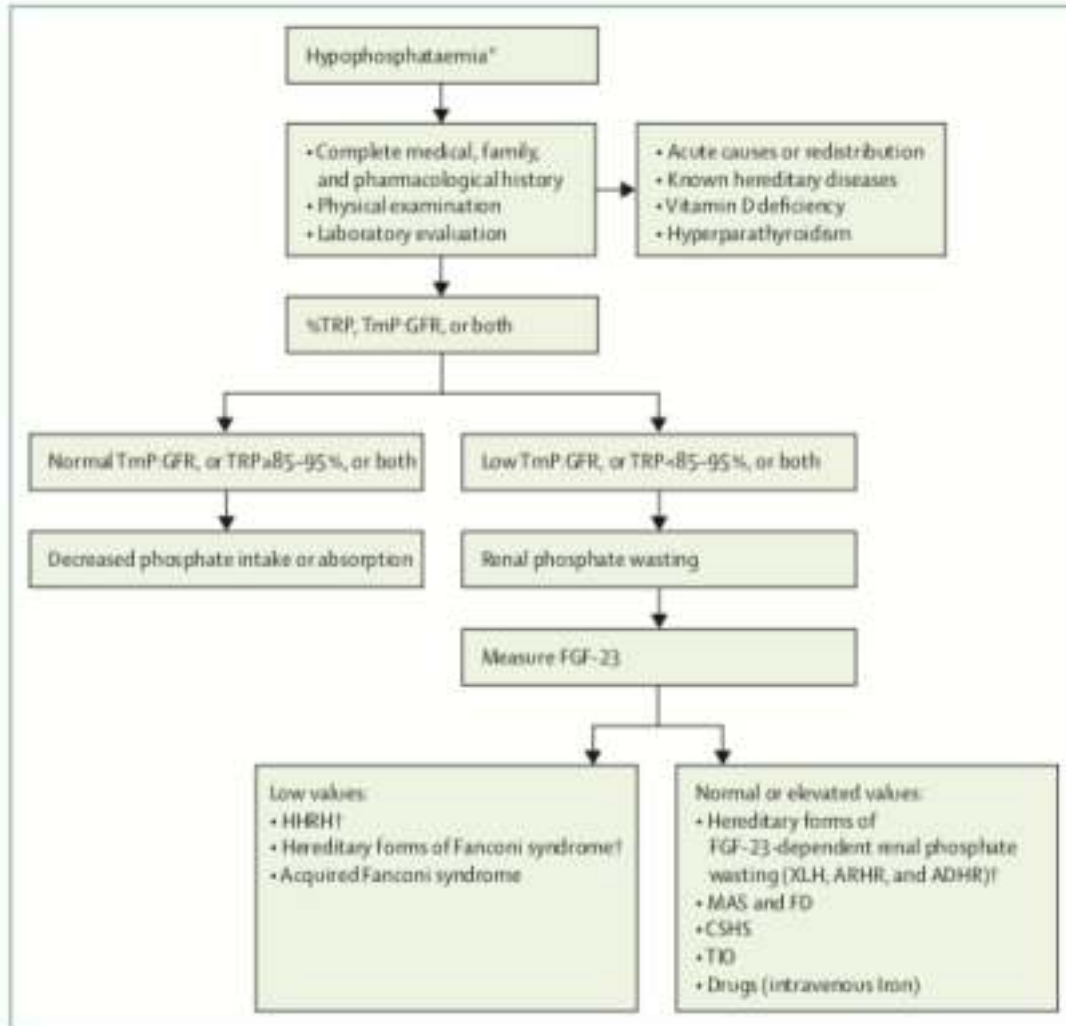
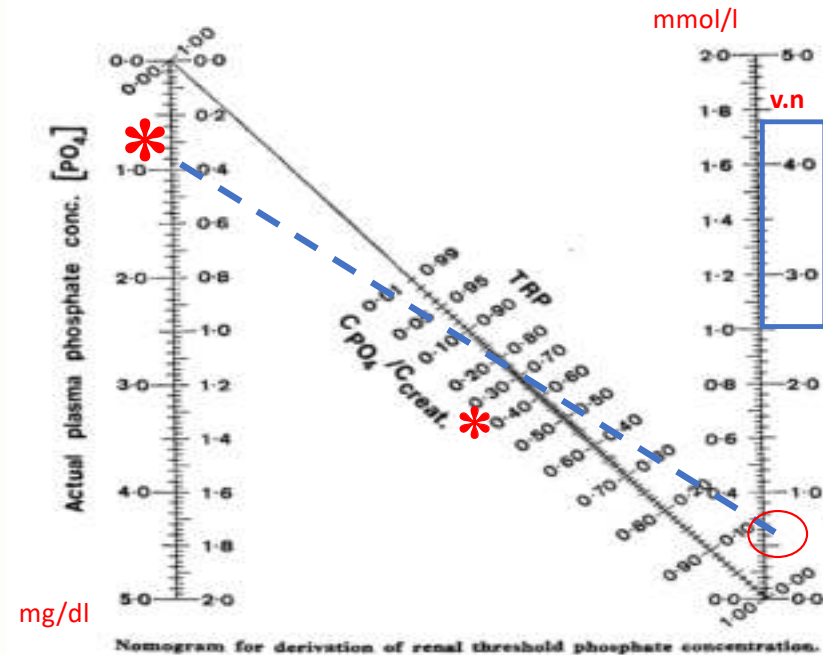


Figure 2: Diagnostic algorithm of hypophosphataemia

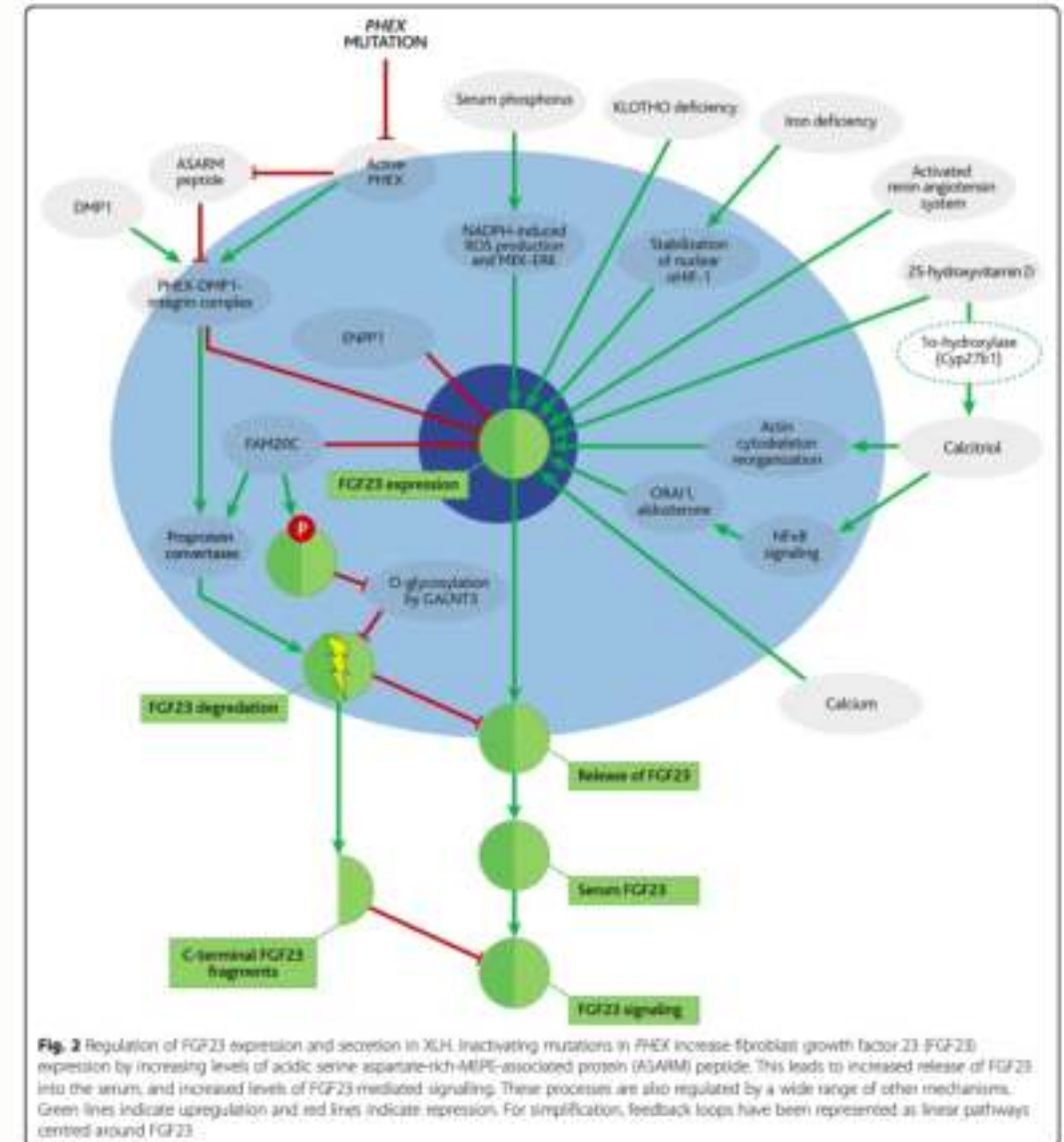
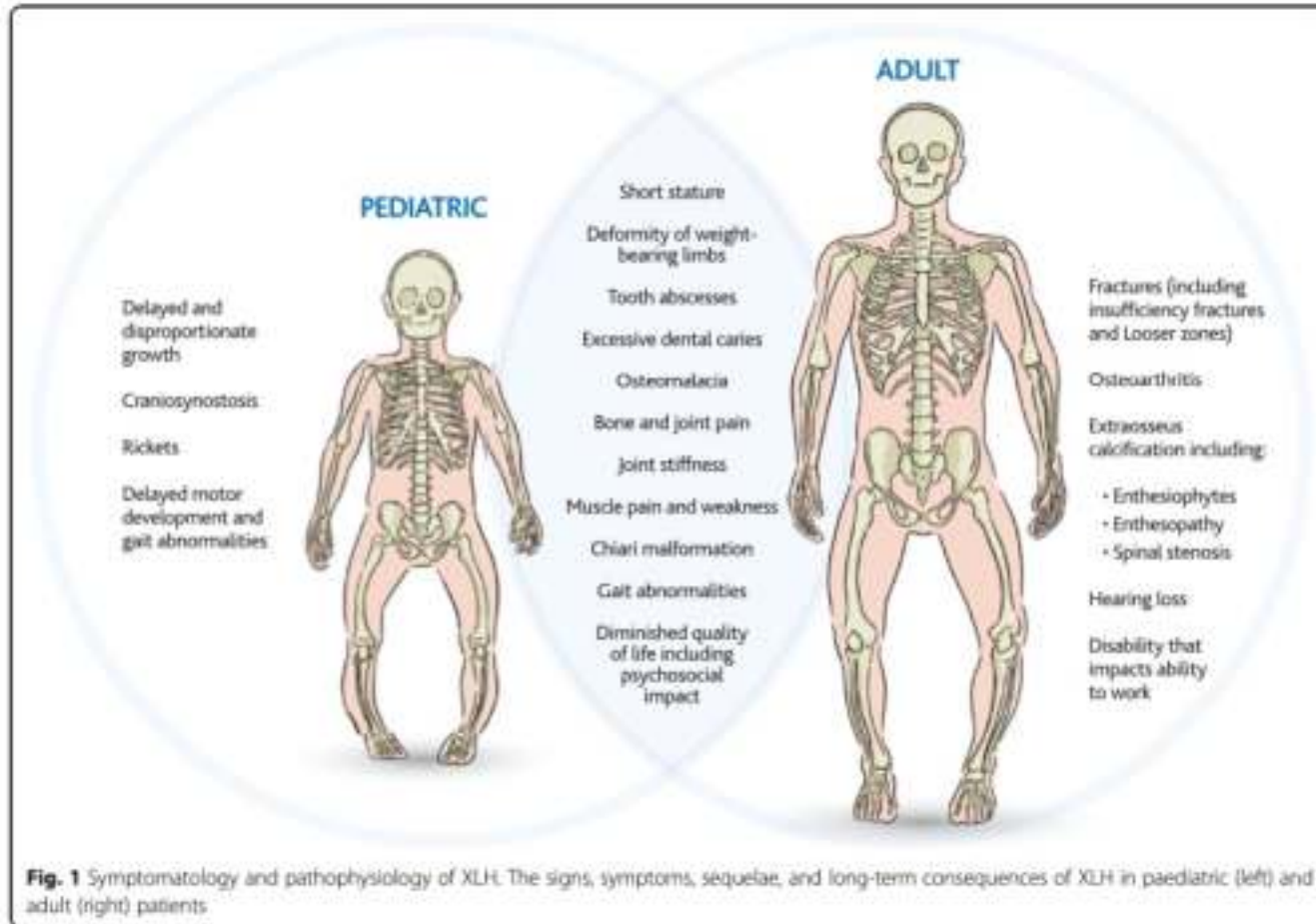
Fosfatemia (mg/dL)	0,9
Fosfaturia (mg/dL)	57,7
Creatininemia (mg/dL)	0,4
Creatininuria (mg/dL)	73,0
Riassorbimento tubulare fosfati (%)	65,2

inserisci i tuoi valori nelle caselle gialle

Nomogramma di Walton e Bijvoet



X-linked hypophosphataemia



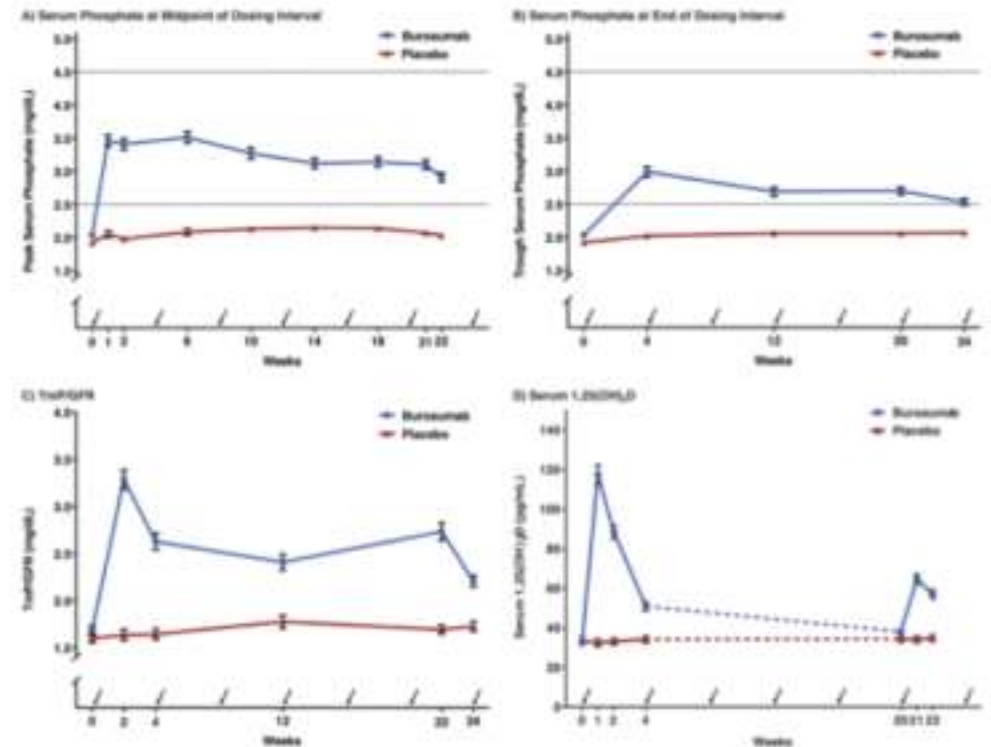
Dalle premesse fisiopatologiche alle applicazioni terapeutiche

CLINICAL TRIAL



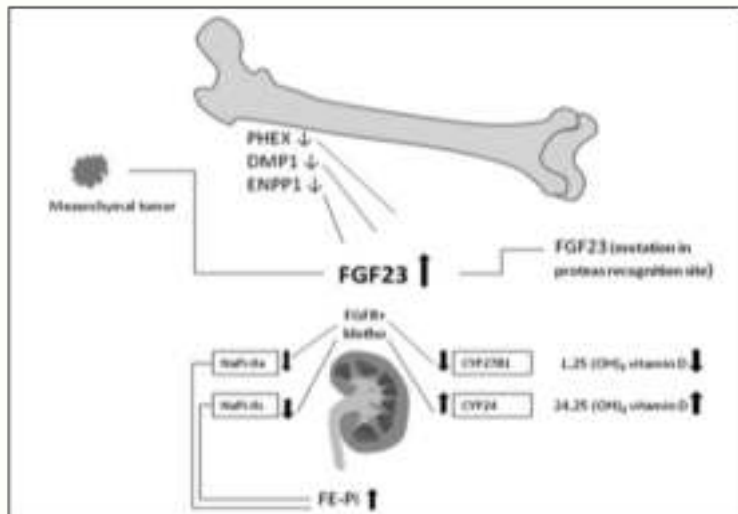
A Randomized, Double-Blind, Placebo-Controlled, Phase 3 Trial Evaluating the Efficacy of Burosumab, an Anti-FGF23 Antibody, in Adults With X-Linked Hypophosphatemia: Week 24 Primary Analysis

Karl L Insogna,¹ Karine Briot,² Erik A Imel,³ Peter Kamenický,⁴ Mary D Ruppe,^{5*} Anthony A Portale,⁶ Thomas Weber,⁷ Pisit Pitukcheewanont,⁸ Hae Il Cheong,⁹ Suzanne Jan de Beur,¹⁰ Yasuo Imanishi,¹¹ Nobuaki Ito,¹² Robin H Lachmann,¹³ Hiroyuki Tanaka,¹⁴ Farzana Perwad,⁶ Lin Zhang,¹⁵ Chao-Yin Chen,¹⁵ Christina Theodore-Oklota,¹⁵ Matt Mealiffe,¹⁵ Javier San Martin,¹⁵ and Thomas O Carpenter¹ on behalf of the AXI FS 1 Investigators



CLASSIFICAZIONE

Phosphaturic mesenchymal tumors of mixed connective tissue variant (*PMTs*)

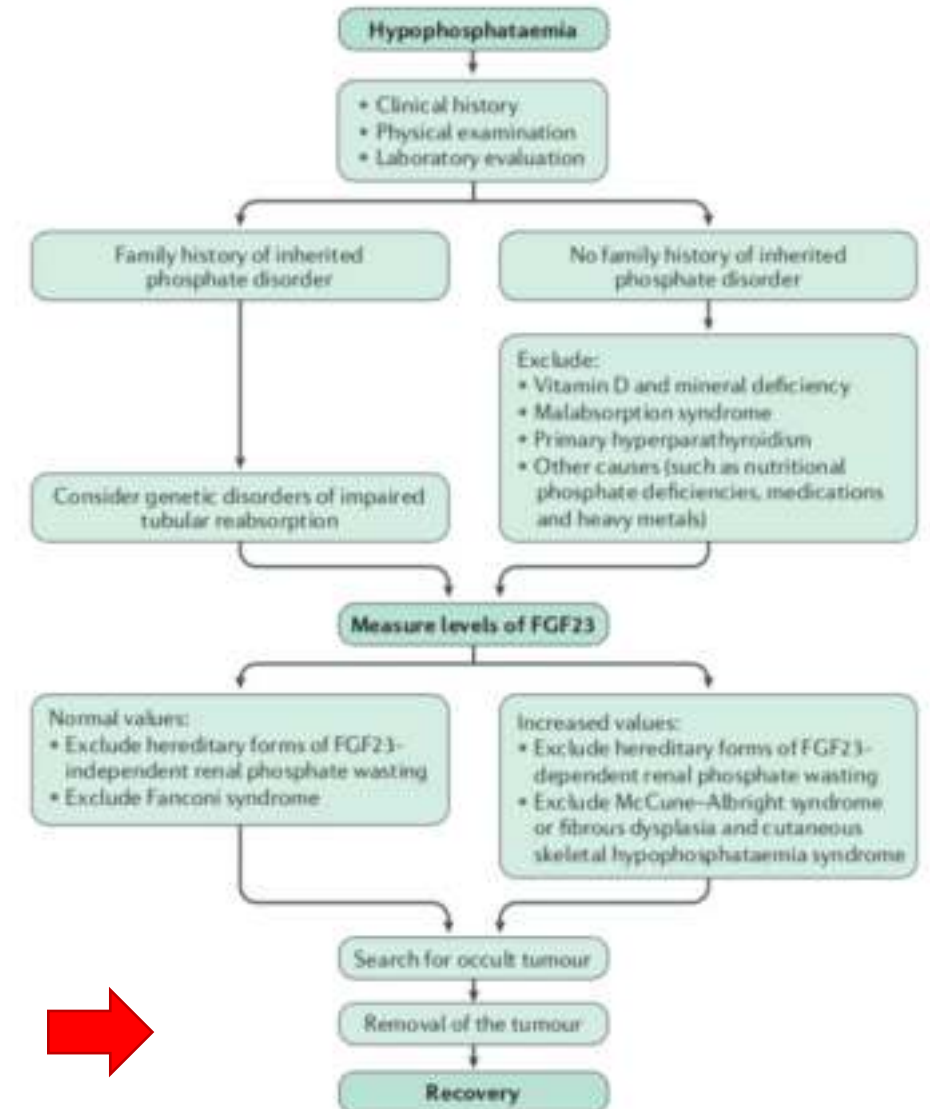


Osteomalacia secondaria

- Neoplasia prostatica
- Microcitoma polmonare
- Discrasie ematologiche
- Neurofibromatosi
- Sindrome del nevo sebaceo
- Displasia fibrosa dell'osso
-

Terapia medica nel TIO: Quando?

- LESIONE TUMORALE NON IDENTIFICABILE
- INTERVENTO CHIRURGICO NON PRATICABILE (*performance status, sede..*)
- **INCOMPLETA RIMOZIONE**
- **RECIDIVE**
- ...

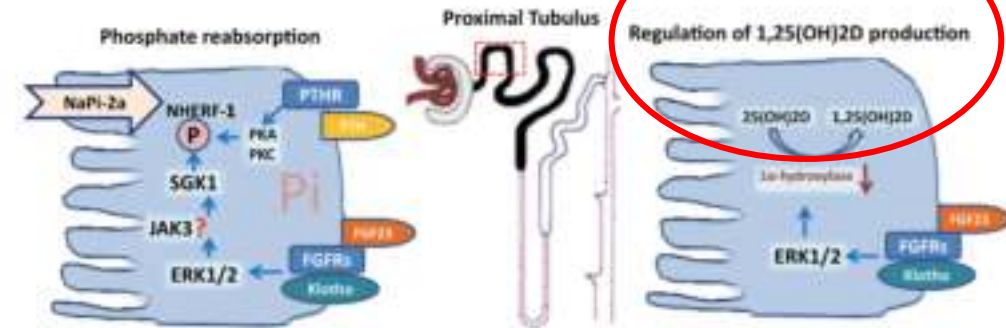
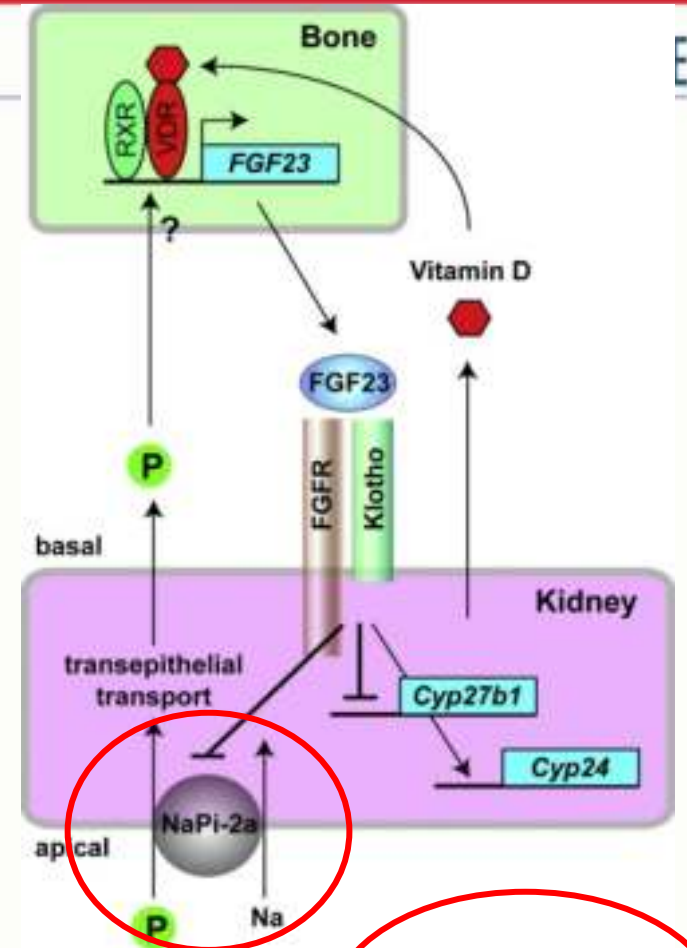


Terapia medica “standard”

- Supplementazione di fosfati e di prodotti attivi di vitamina D

- Sali di fosfato 20-40 mg/kg/die a dosi refratte
- Calcitriolo 20-30 ng/Kg/die
- ALTERNATIVAMENTE ALFACALIDILOLO

TITOLAZIONE DELLA TERAPIA



TERAPIA STANDARD: pros and cons

VANTAGGI:

- BASSO COSTO
- CONTROLLO DELLA SINTOMATOLOGIA
(astenia, dolore)
- ...

LIMITI:

- PROBLEMATICHE GASTROINTESTINALI
- IPERCALCEMIA
- NEFROCALCINOSI
- IPERPARATIROIDISMO SECONDARIO → TERZIARIO
- COMPARTECIPE DEL RITARDO DIAGNOSTICO

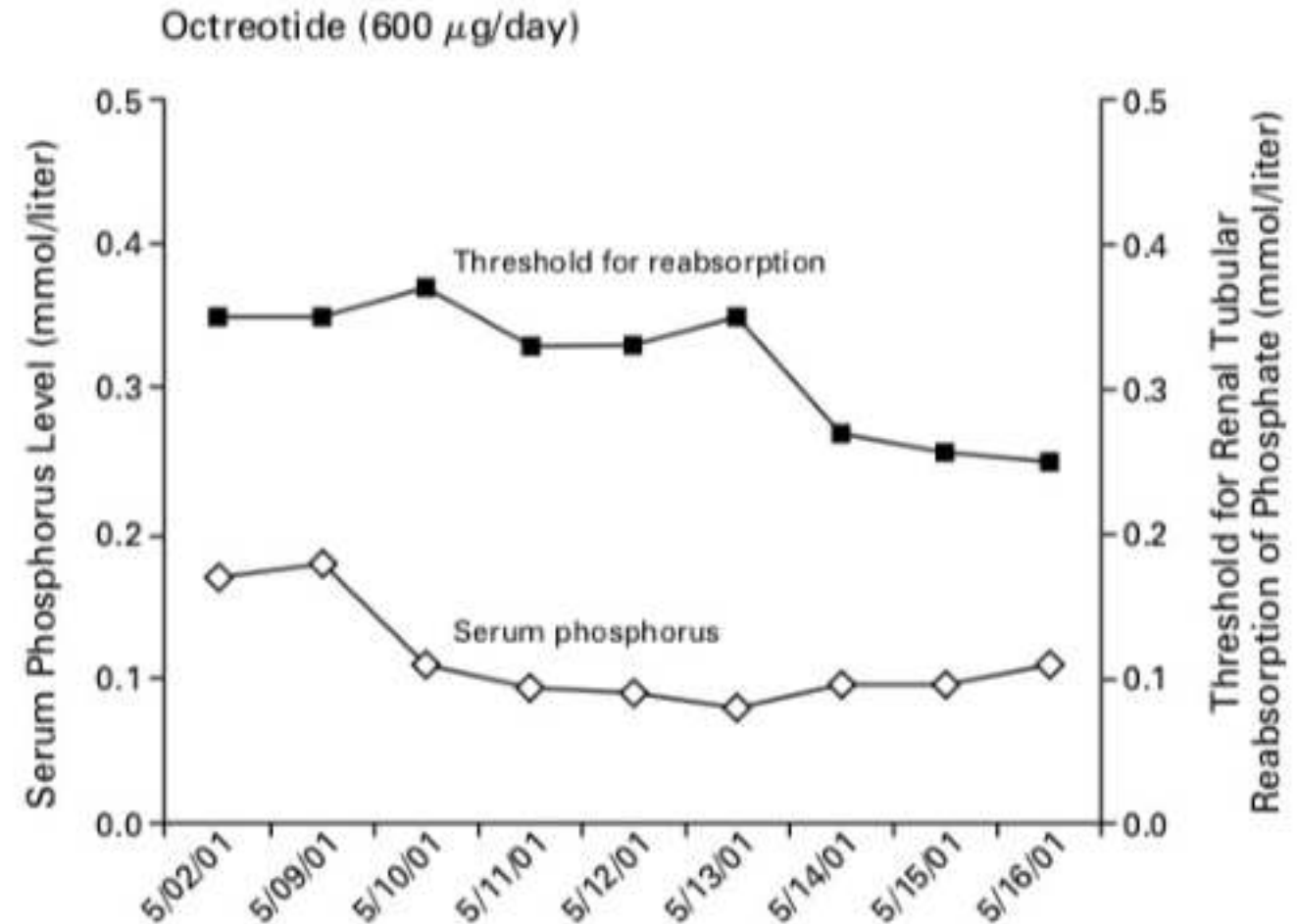
ANALOGHI DELLA SOMATOSTATINA E TIO

- RAZIONALE: espressione recettoriale della Somatostatina nei tumori fosfaturici (SSTR)

CONCLUSIONI:


Octreotide non rappresenta una terapia efficace per la soppressione di FGF 23

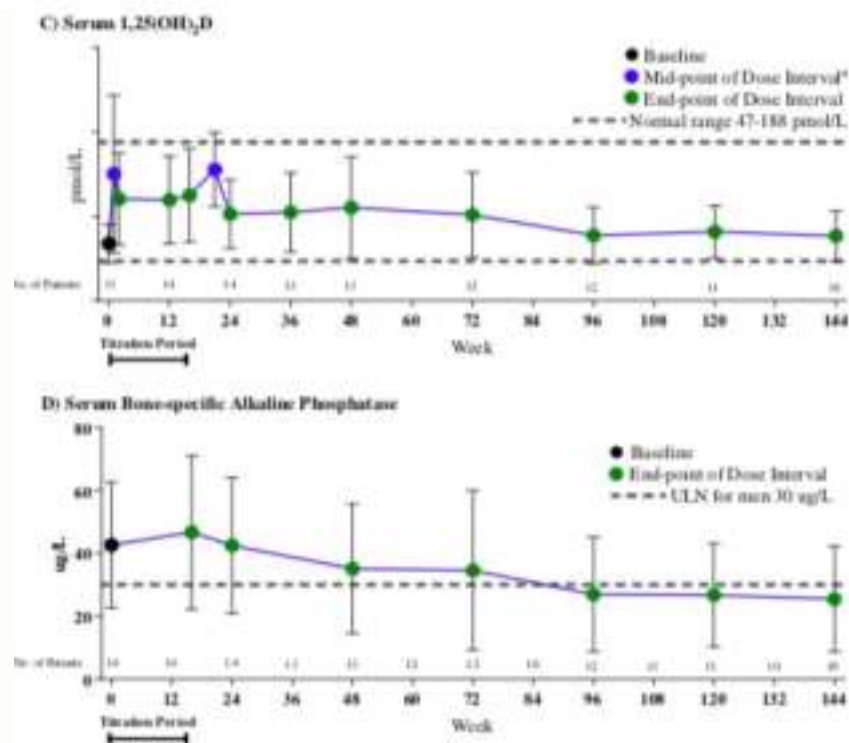
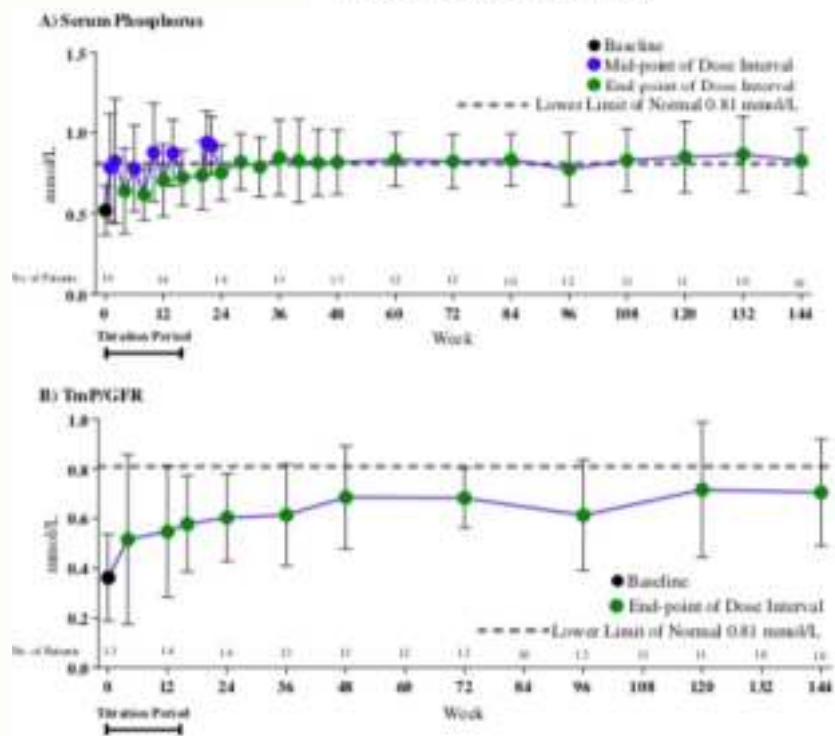
- Differenti sottotipi patogenetici coinvolti nella neoplasia?



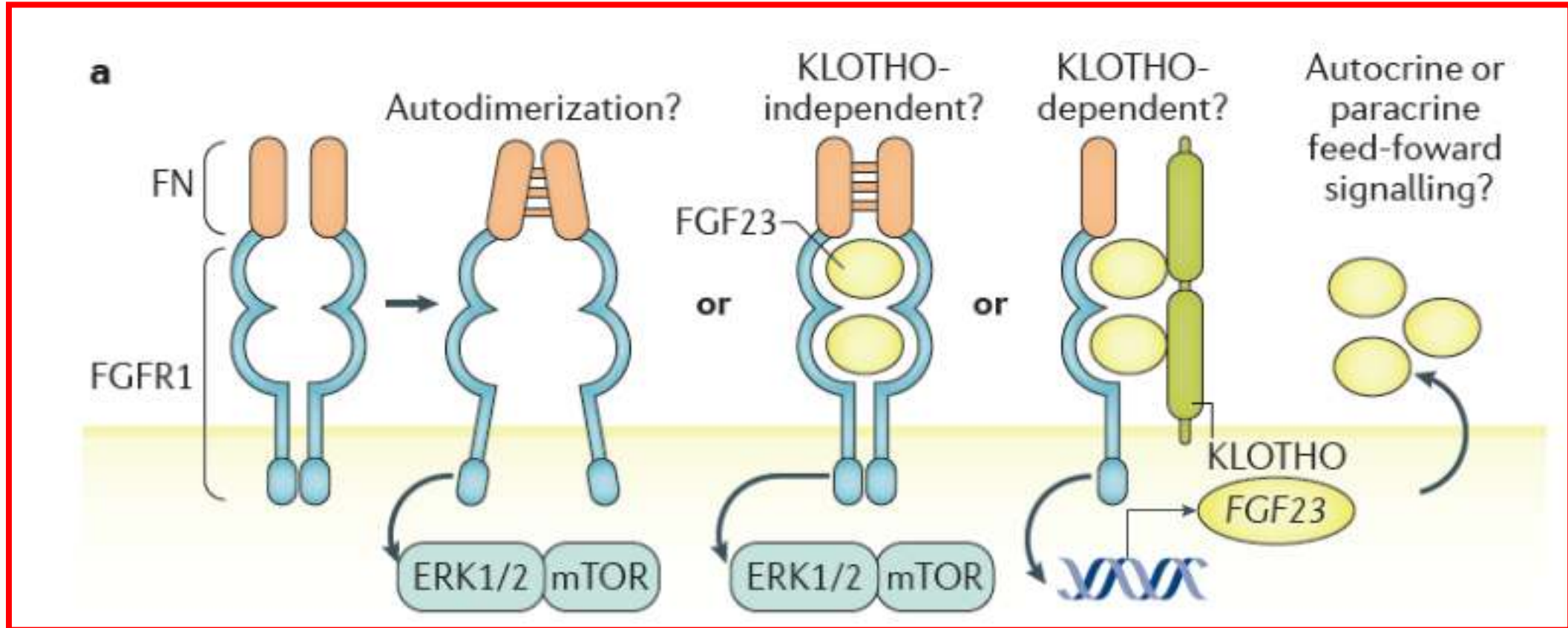
CLINICAL TRIAL

Burosumab for the Treatment of Tumor-Induced Osteomalacia

Suzanne M Jan de Beur,¹ Paul D Miller,² Thomas J Weber,³ Munro Peacock,⁴ Karl Insogna,⁵  Rajiv Kumar,⁶ Frank Rauch,⁷ Diana Luca,⁸ Tricia Cimms,⁸ Mary Scott Roberts,⁸ Javier San Martin,⁸ and Thomas O Carpenter⁵



FN1-FGFR1 TRANSLOCATIONS

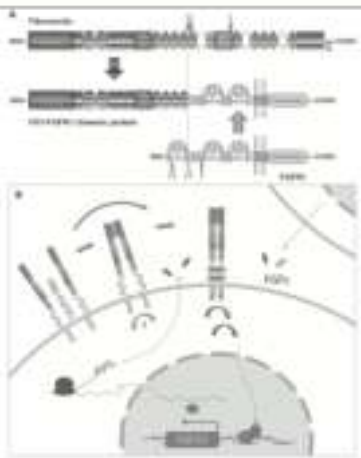


Lee JC, *J Pathol* 235:539–545

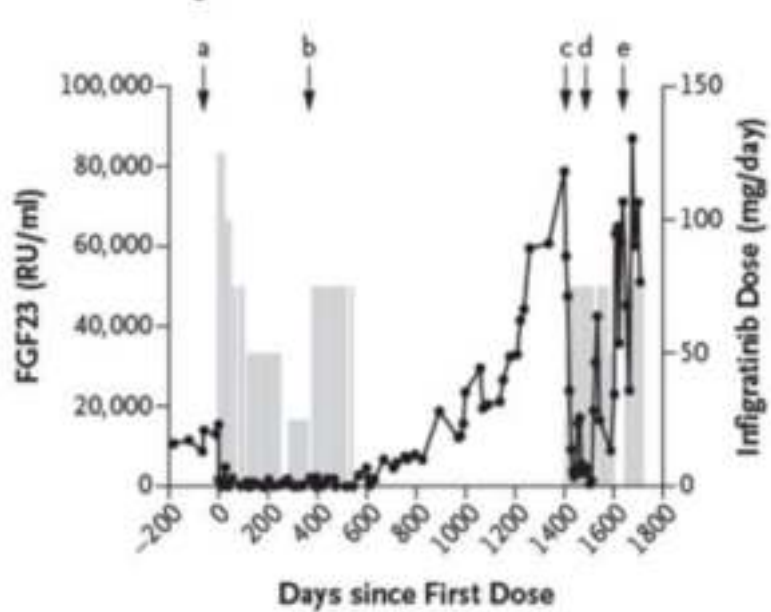
Minisola S., et al. *Nature R.D.P.*, 2017

Infigratinib: risposta al trattamento

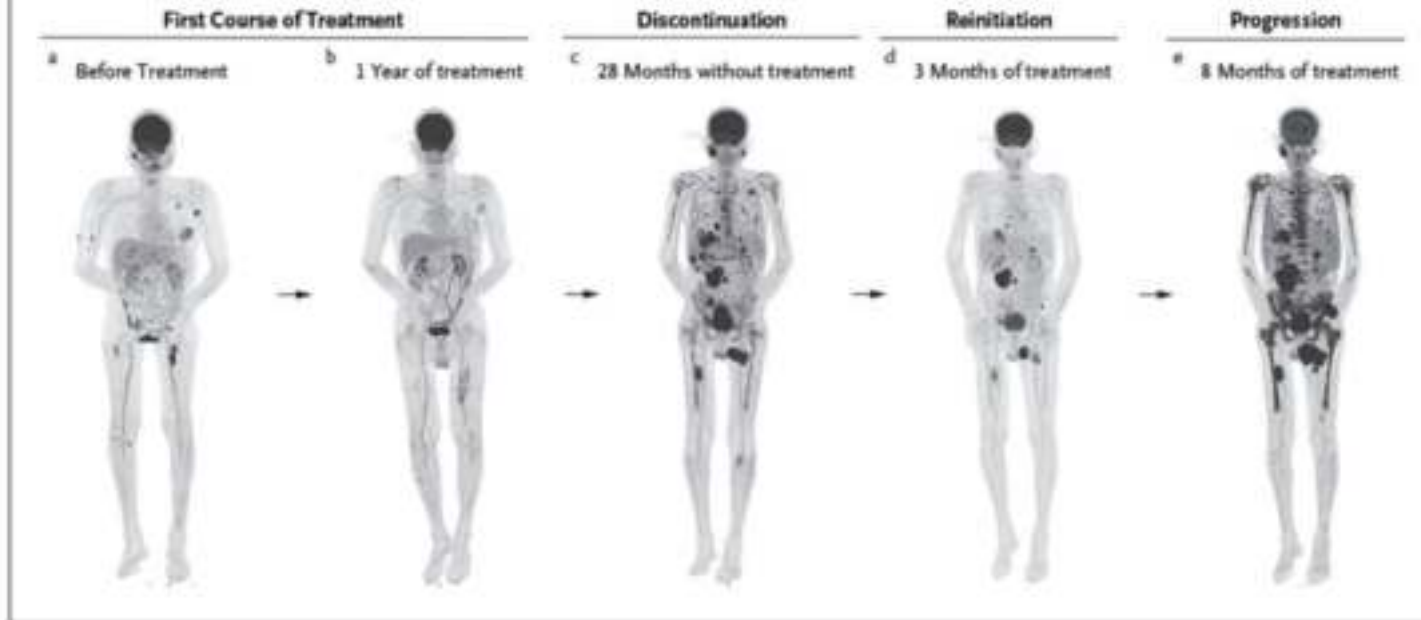
Pan-FGFr tyrosine kinase inhibitor
(BGJ398/infigratinib)



A Effect of Infigratinib on FGF23 Levels



C Whole-body ¹⁸F-FDG-PET-CT

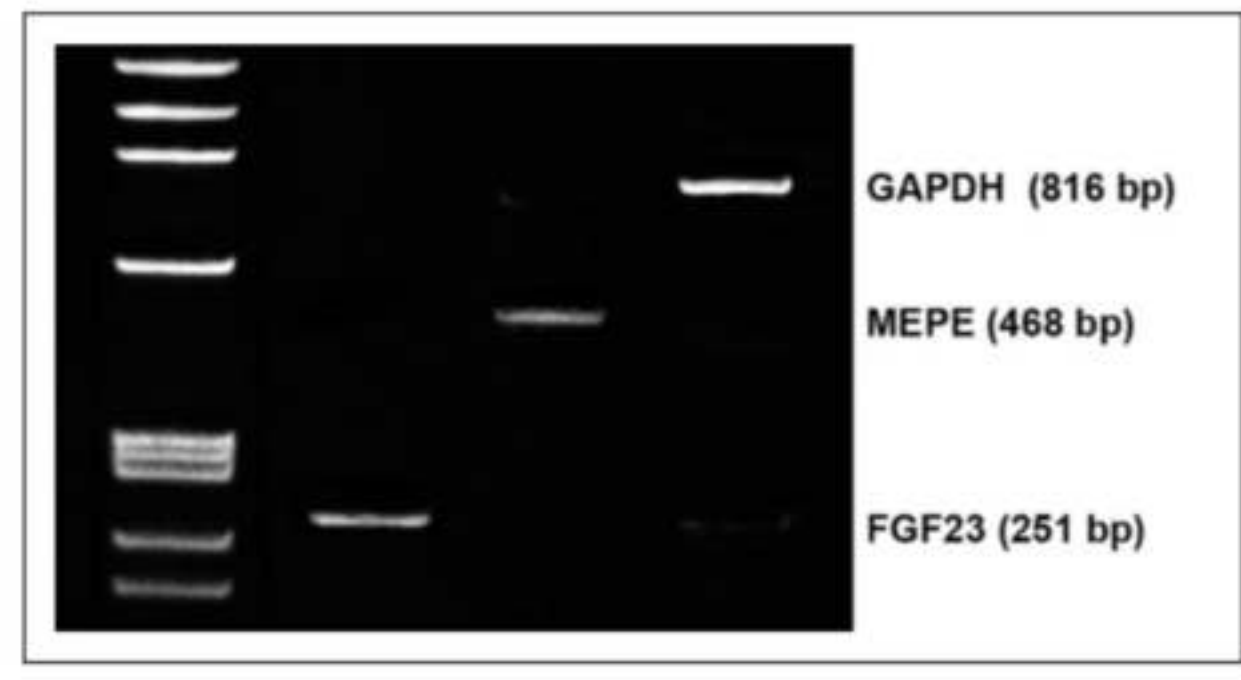
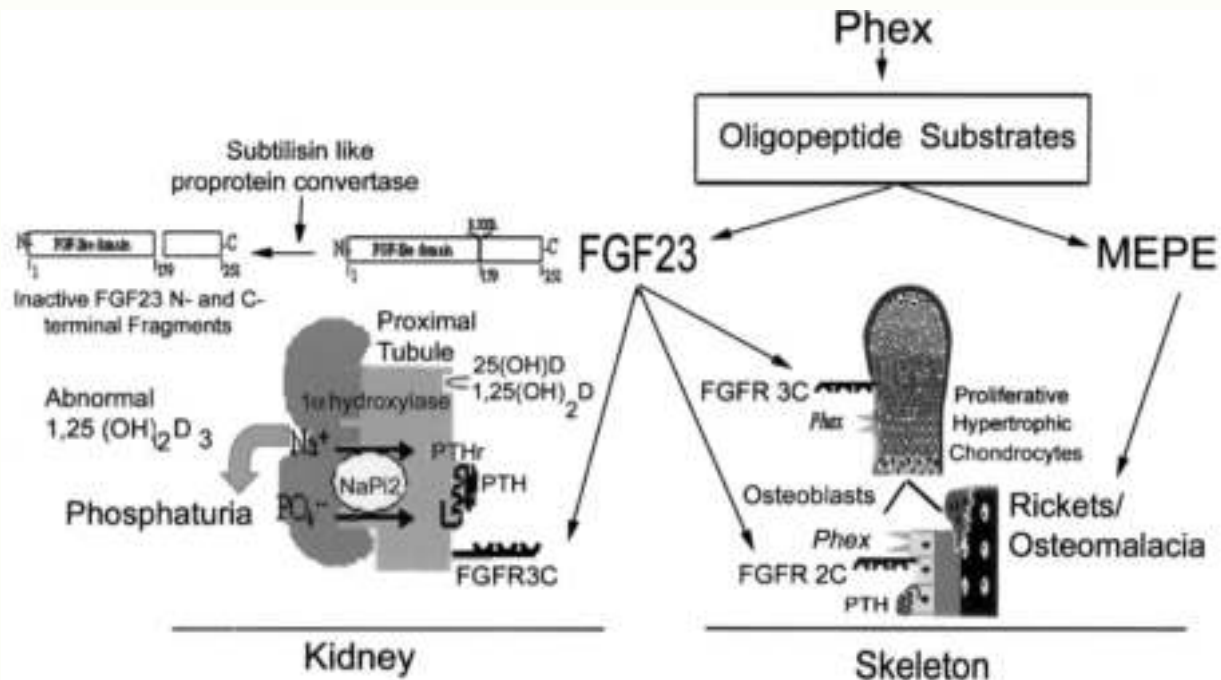


LIMITI ATTUALI DI TALE TERAPIA:

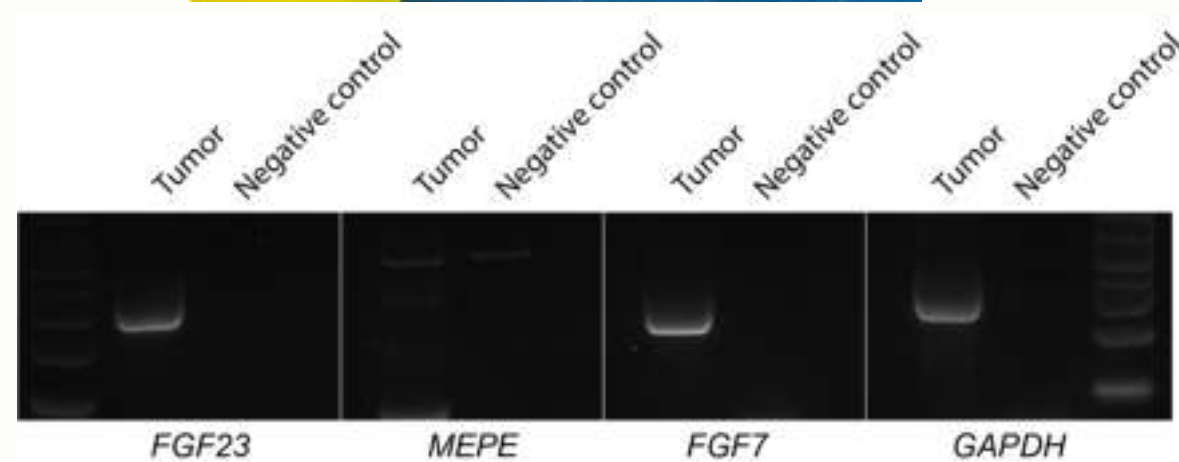
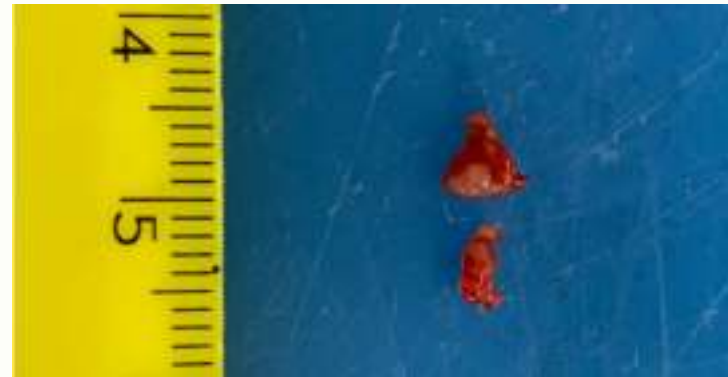
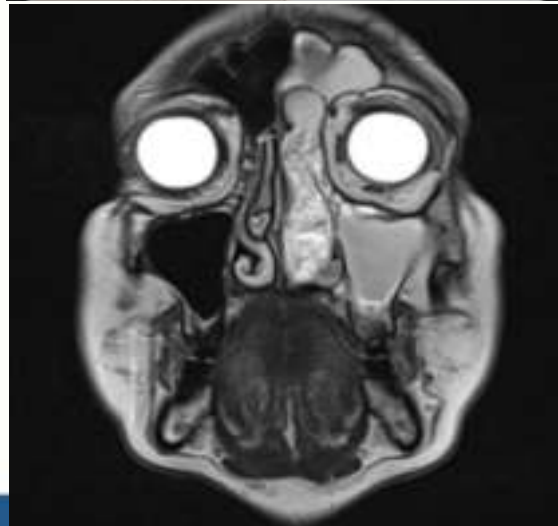
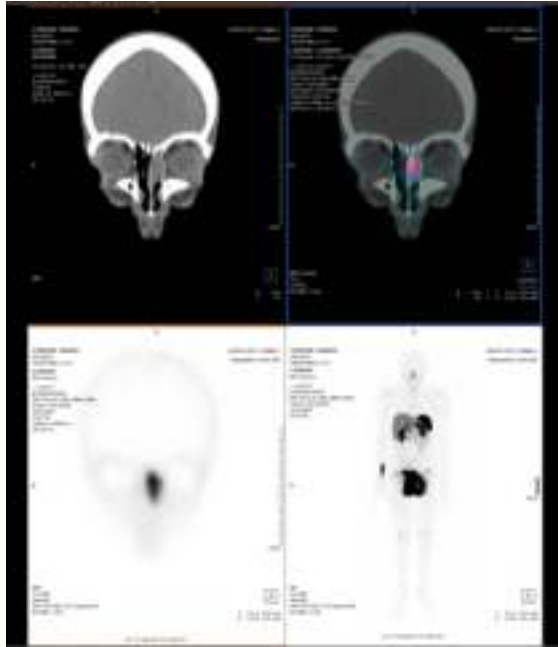
Effetti collaterali

Promessa: Seconda generazione di pan-FGFR inhibitor

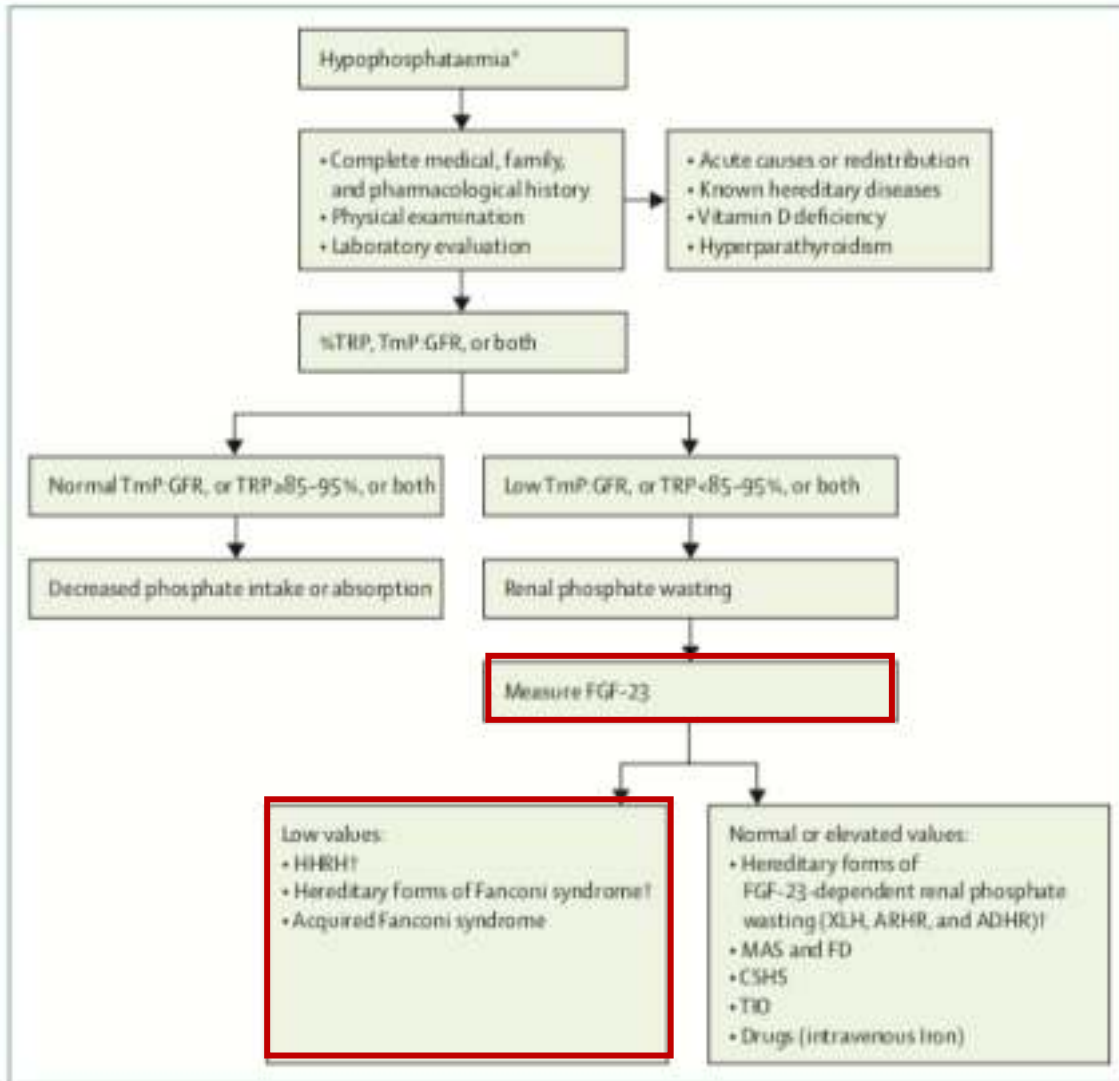
ALTRE FOSFATONINE: CONSIDERAZIONI TERAPEUTICHE I



ALTRE FOSFATONINE: CONSIDERAZIONI TERAPEUTICHE II



Non-FGF23 mediated causes of hypophosphatemia



- HHRH
- Acquired Fanconi Syndrome (cisplatino, antivirali, gammopatie monoclonali...)

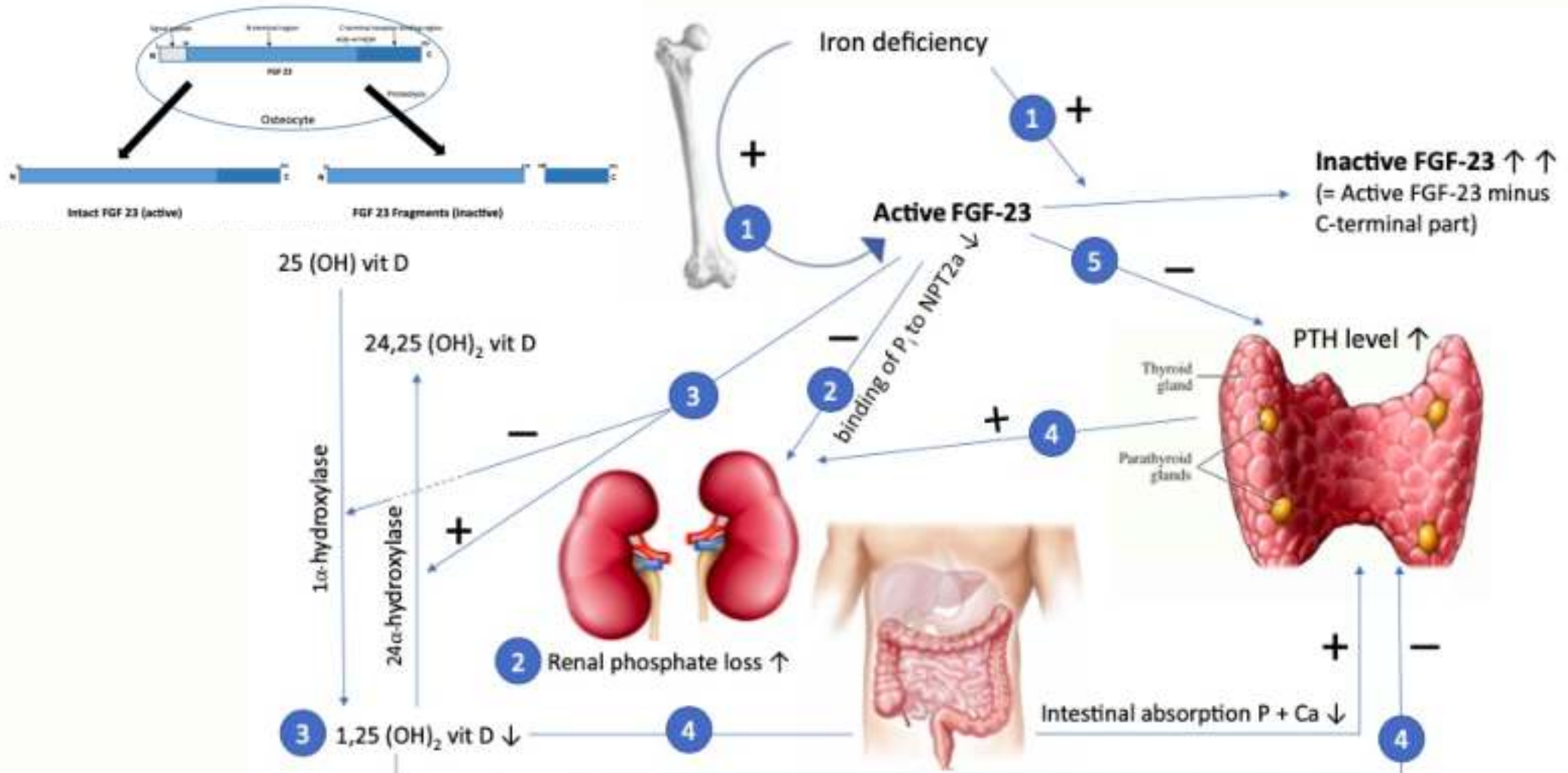
Clin Rheumatol (2016) 35:1271–1279
DOI 10.1007/s10067-014-2627-x

ORIGINAL ARTICLE

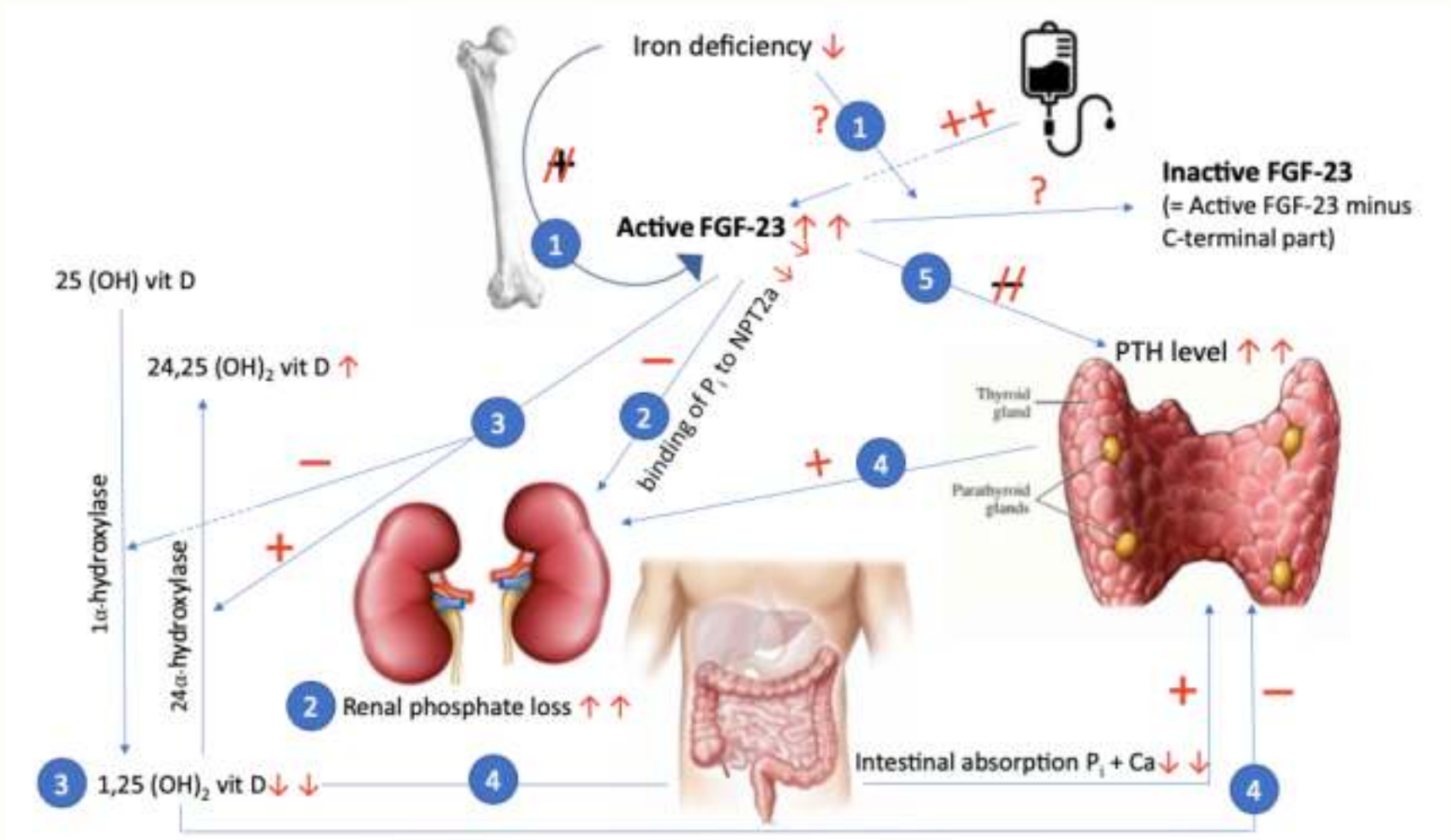
Hypophosphatemic osteomalacia induced by tenofovir in HIV-infected patients

Recently, the use of **Tenofovir alafenamide** (TAF), a new prodrug of tenofovir, has been reported to be significantly less harmful compared to **Tenofovir disoproxil fumarate** (TDF).

FGF23 AND IRON DEFICIENCY



FGF23 AFTER INFUSION OF FERRIC CARBOXYMALTOSE



Osteomalacia as a Complication of Intravenous Iron Infusion: A Systematic Review of Case Reports

Tatiane Vilaca,¹ Nalini Velmurugan,² Christopher Smith,³ Bo Abrahamsen,^{2,3,4} and Richard Eastell¹

¹Department of Oncology and Metabolism, University of Sheffield, Sheffield, UK

²Department of Medicine, Holbæk Hospital, Holbæk, Denmark

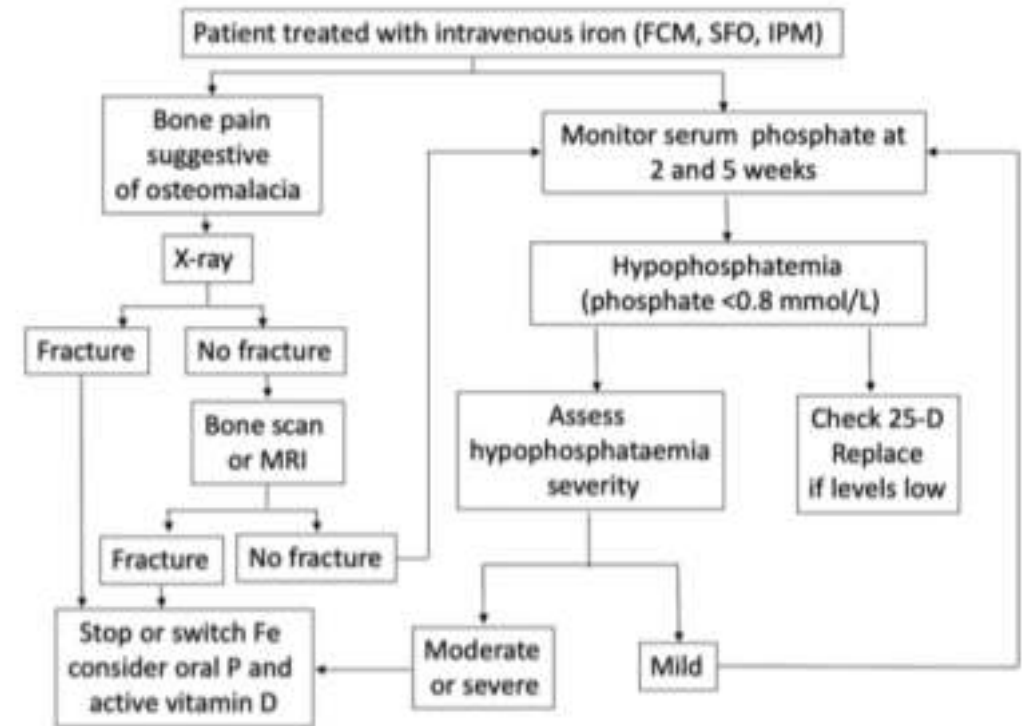
³Open Patient Data Explorative Network, Department of Clinical Research, University of Southern Denmark, Odense, Denmark

⁴Denmark and NDORMS, University of Oxford, Oxford, UK

The lowest phosphate level reported in each case ranged from 0.16 to 0.77 mmol/L

In all the 15 cases where iFGF23 level was measured, it was high (1.6 to 7.8 times)

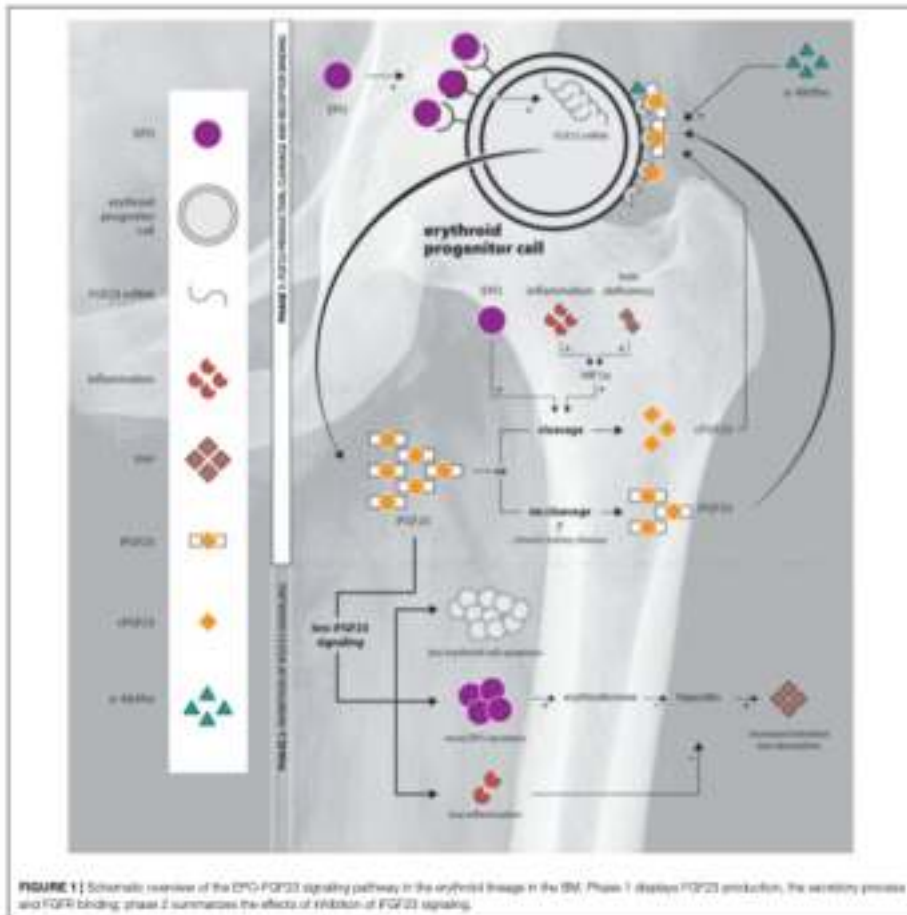
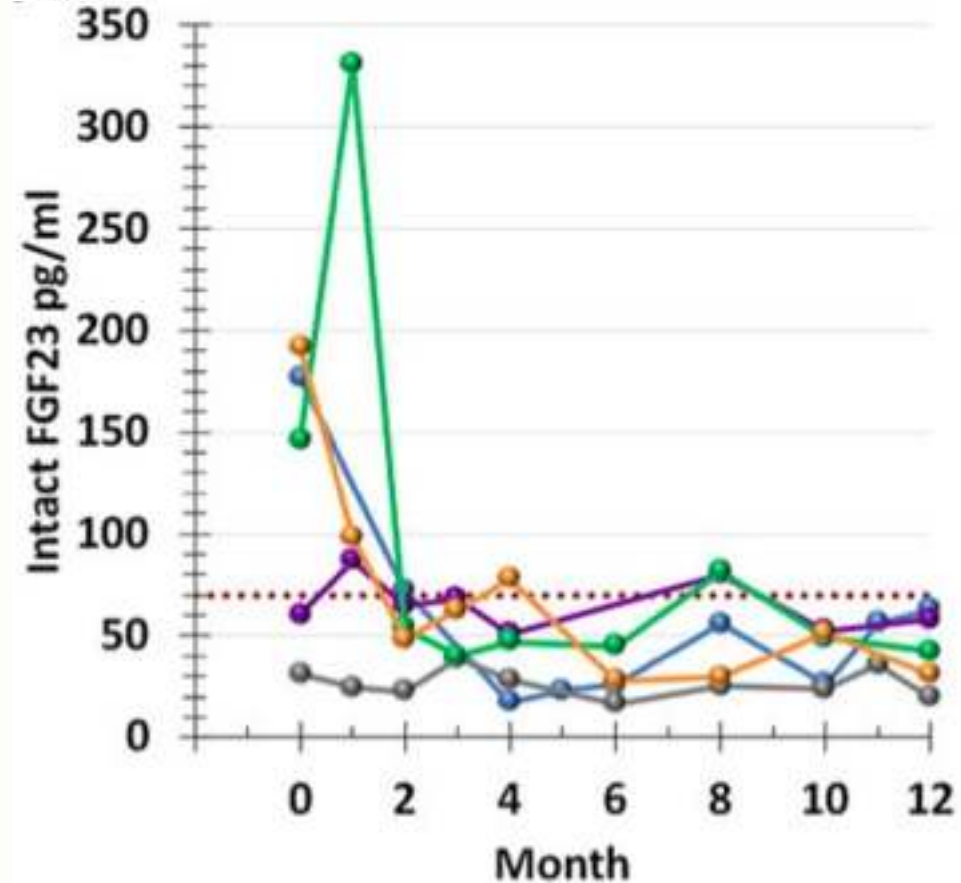
Twenty patients had pseudofractures (14 of the chest 14 of the lower limbs 7 of the pelvis, and 1 of the upper limb) Nine patients had fractures (7 of the lower limbs, 6 of the pelvis, 4 of the ribs, and 3 of the vertebra)



IRON AND FGF23: a new area of research

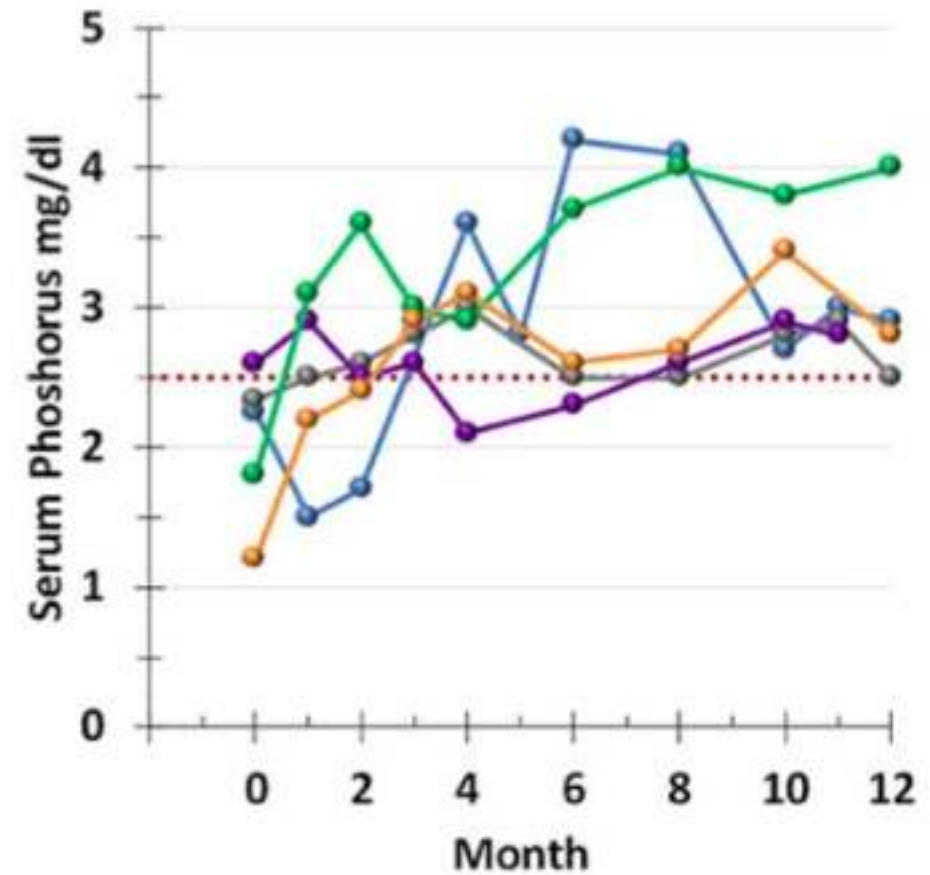
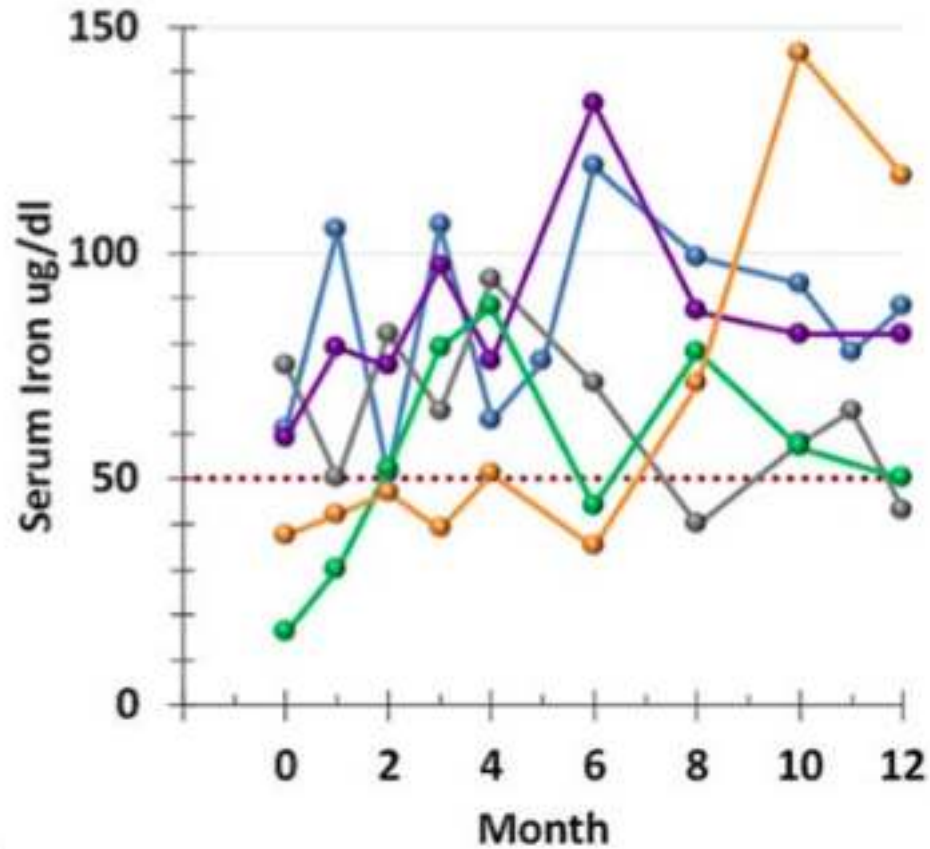
Oral Iron Replacement Normalizes Fibroblast Growth Factor 23 in Iron Deficient Patients with Autosomal Dominant Hypophosphatemic Rickets

Erik A. Imel^{1,2}, Ziyue Liu³, Melissa Coffman¹, Dena Acton¹, Rakesh Mehta¹, Michael J. Econs^{1,4}

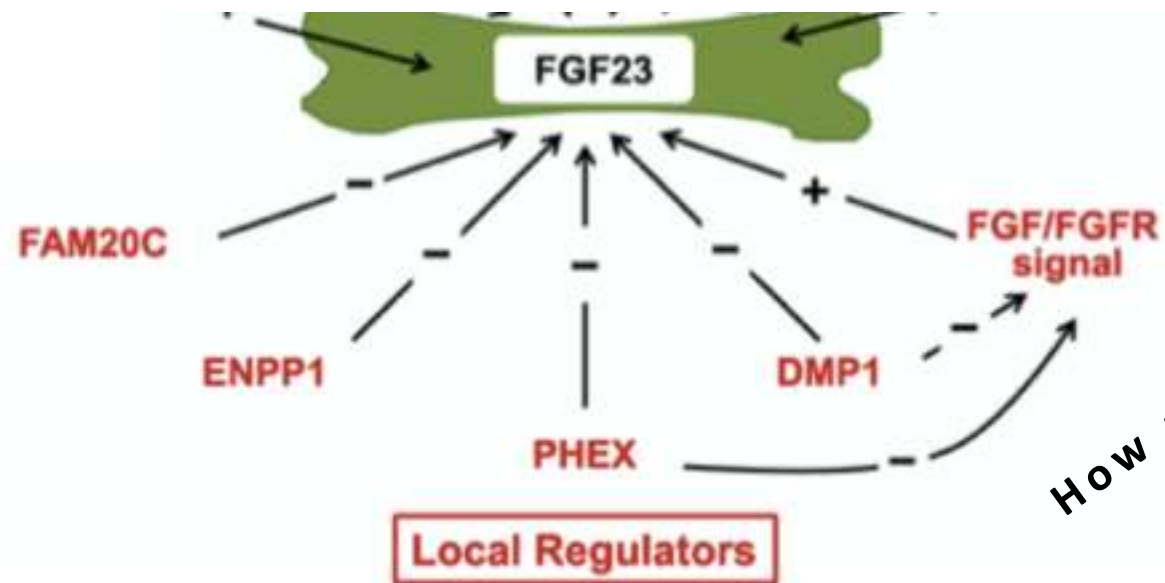


Oral Iron Replacement Normalizes Fibroblast Growth Factor 23 in Iron Deficient Patients with Autosomal Dominant Hypophosphatemic Rickets

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Advances in understanding of phosphate homeostasis and related disorders



How are Pi levels sensed?

Take home messages

- L'ipofosfatemia è un rilievo biochimico spesso ignorato e/o sottovalutato
- Il suo corretto inquadramento diagnostico rappresenta un elemento indispensabile per un approccio terapeutico efficace
- Disponibilità di nuove strategie terapeutiche
- Future directions: comprensione dei vari fattori regolatori dell'FGF23