38 year old Male with Ankylosing Spondylitis

Olesya Krivospitskaya, MD

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HPI (Letter from the patient):

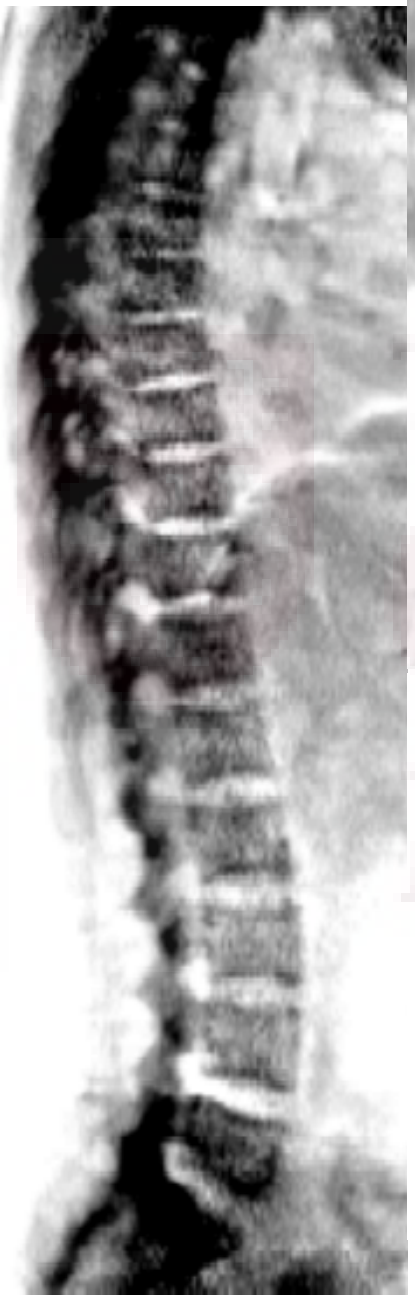
Diagnosed with Ankylosing Spondylitis and prescribed a Sulfa drug to help with my back pain in July 2010. After a month I was admitted with D.R.E.S.S. Syndrome. XXX prescribed Prednisone from September of 2011 till January of 2012. XXX prescribed Indomethacin since February 2012 adding Enbrel for a few months before switching to Humira about six months ago. Because of continued pain in both legs and a lack of progress I switched to my current rheumatologist in December 2012 who diagnosed me with a severe lack of bone density.

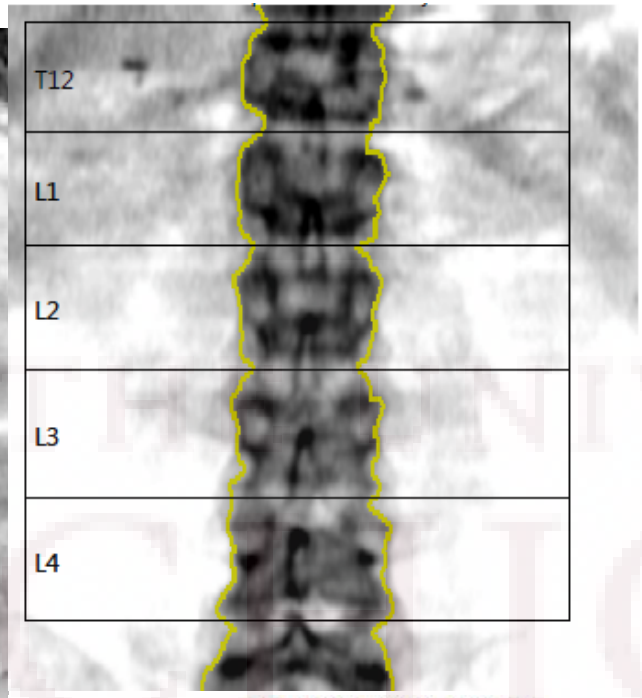
The last 2 years have been specially hard. I am only 38 years old and I wish to walk without a cane, avoid disability, and have a normal life. My need is not only for my health but also for the future of my wife and kids.

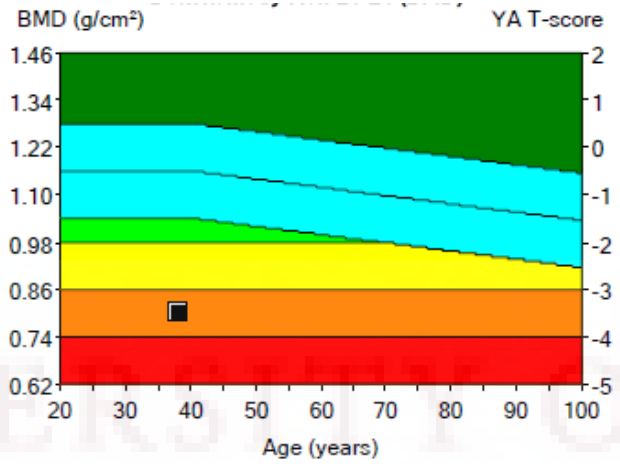
HPI:

- Bone scan in 12/2012 showed pathologic fractures in his ribs, head of the L femor, neck of the R femur, medial condyles of the femoral bone and tibia bilaterally, distal diaphysis of tibiae bilaterally

- BMD in 12/2012 showed L-spine T-score of -4.1, Z-score -4.0, total hip T-score -6.1, Z-score -5.7.

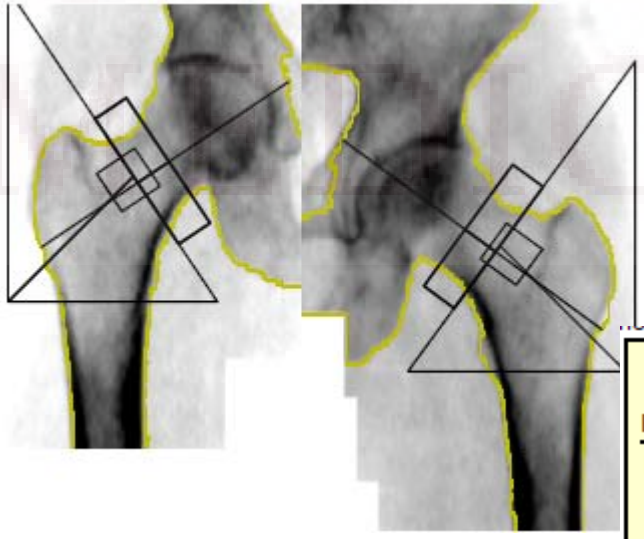


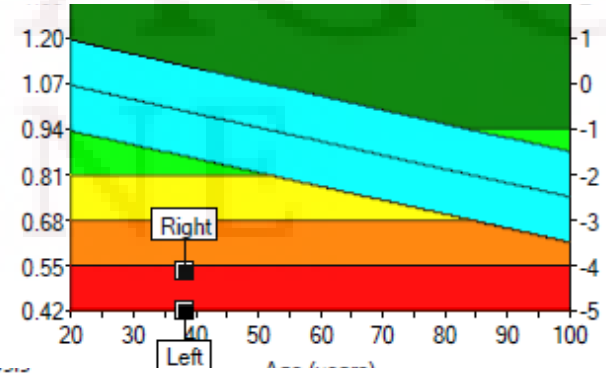




Region	BMD (g/cm²) [1]	Young-Adult T-score [2]	Age-Matched Z-score [3]
L1-L4	0.802	-3.5	-3.0

DualFemur Bone Density





Region	BMD (g/cm²) [1]	Young-Adult T-score [2,7]	Age-Matched Z-score [3]
Neck			
Left	0.422	-5.0	-4.4
Right	0.535	-4.1	-3.5

HPI:

- More history
  - Used to be an athlete
  - Walks with cane
  - bone scan: 12/2012, pathologic fractures ribs, head of the L femur, neck of the R femur, medial condyles of the femora and tibia bilaterally, distal diaphysis of tibiae bilaterally.
- Physical exam
  - Vitals: 127/86, HR 71, Ht 162.6cm, Wt 64.2kg, BMI 24.29
  - Looks healthy but uncomfortable
  - Can't get up from chair
  - Can't get on the table un-assisted

- ***PMH:***

  Ankylosing spondylitis

  DRESS syndrome

- ***Surgical hx:***

  Cholecystectomy in 09/2011

- ***Social hx:***

  Former professional boxer and runner, works in car sales, married, has 3 kids (12, 11 and 9 years old). Does not smoke, drink or use any illigal drugs.

- ***Family hx:***

  No history of fractures or osteoporosis in his family

Medications:

- CALCIUM 600 + D(3) BID
- indomethacin 50 mg TID as needed for pain

- What do you think is going on?
- Why is his BMD so low? Steroids?
- What labs would you get?

Labs:

140	106	12	85
3.9	24	0.8	

Ca 9.0 (8.4-10.2 mg/dL),

LFTs:

Total Protein 7.7 (6-8.3 g/dL)

Albumin 4.8 (3.5-6 g/dL)

Total Bilirubin 0.5 (0.1-1 mg/dL)

Alk Phos 488 (30-120 U/L)

AST 17 (8-37 U/L)

ALT 19 (8-35 U/L)

PTH 41 (15-75 pg/mL)

25-hydroxy vitamin D 27 ng/mL

1,25 vitamin D 15 (18-64 pg/mL)

Bone specific Alk Phos 162 (0-20 mcg/L)

Phos 1.4 (2.5-4.4 mg/dL)

FGF23 145 (<=180 RU/mL) from 01/11/2013

FGF23 180 (<=180 RU/mL) from 02/15/2013

- What would be a differential?
- What other labs could help?

Differential in this case:

- Vitamin D resistance
- Tumor induced osteomalacia
- Hypophophatemic rickets
- Fanconi syndrome

Labs:

Protein electrophoresis:

No monoclonal proteins detected by routine protein electrophoresis

UA (random):

Specific gravity 1.012,
pH 6.5,
LE neg,
nitrate neg,
protein neg,
glucose trace,
blood trace,
ketones neg,
bilirubin neg,
RBC 3 to 5,
WBC none,
calcium <1 mg/dL,
phos 63.7 mg/dL
creatinine 62 mg/dL

- The pt was started on K-Phos 1000mg TID and calcitriol 0.5mcg TID

- Repeat labs from 01/24/2013 showed:

140	107	13	92
3.7	26	0.7	

Ca 8.4 (8.4-10.2 mg/dL),

Phos 1.4 -> 1.8 (2.5-4.4 mg/dL)

- K-phos was increased to 2000mg TID, continue calcitriol 0,5mcg TID

- Repeat labs from 04/03/2013 showed:

139	104	12
4.0	24	0.7

84

Ca 8.5 (8.4-10.2 mg/dL),

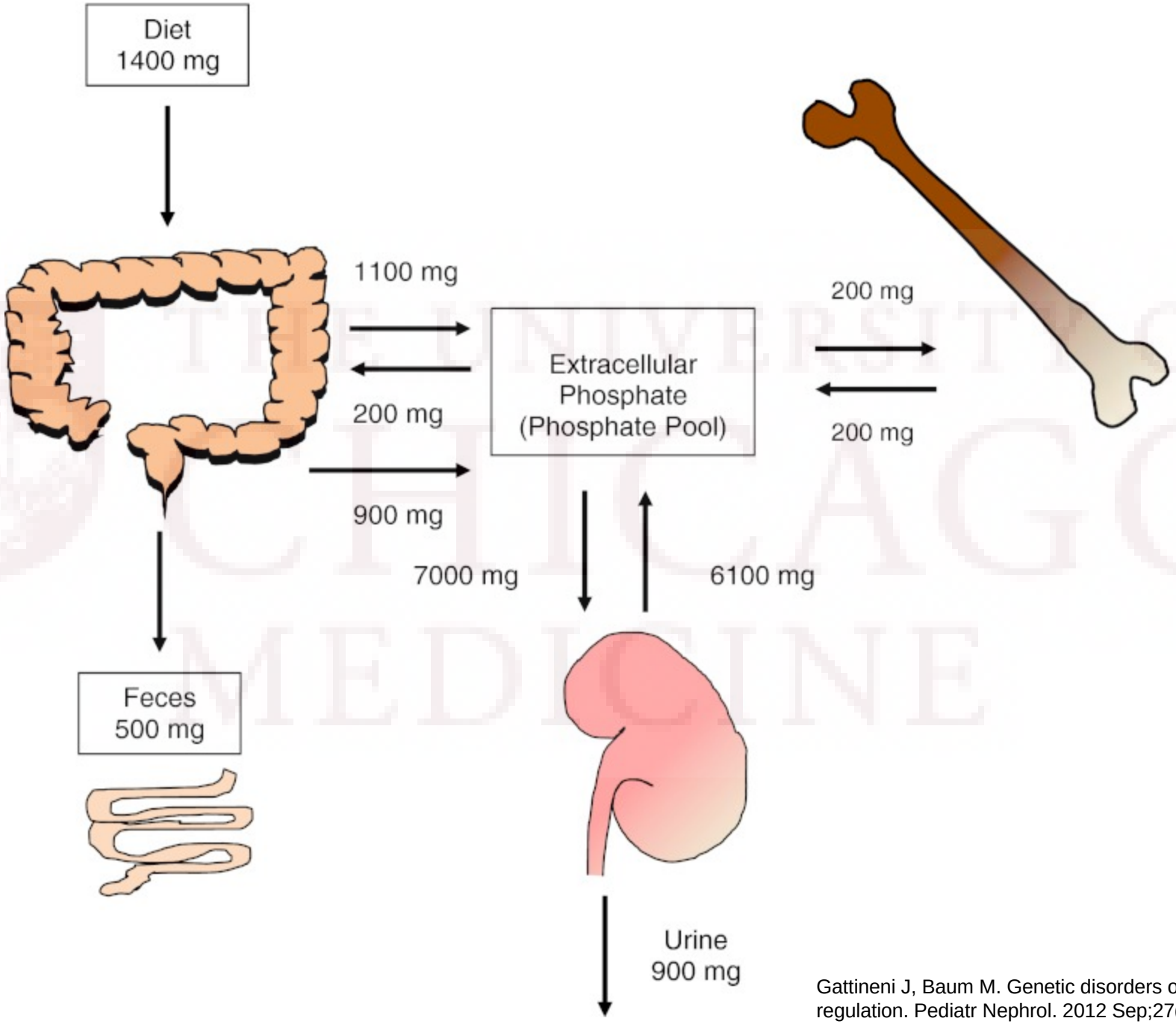
Phos 1.4 -> 1.8 -> 2.0 (2.5-4.4 mg/dL)

Albumin 4.6 (3.5-5 g/dL)

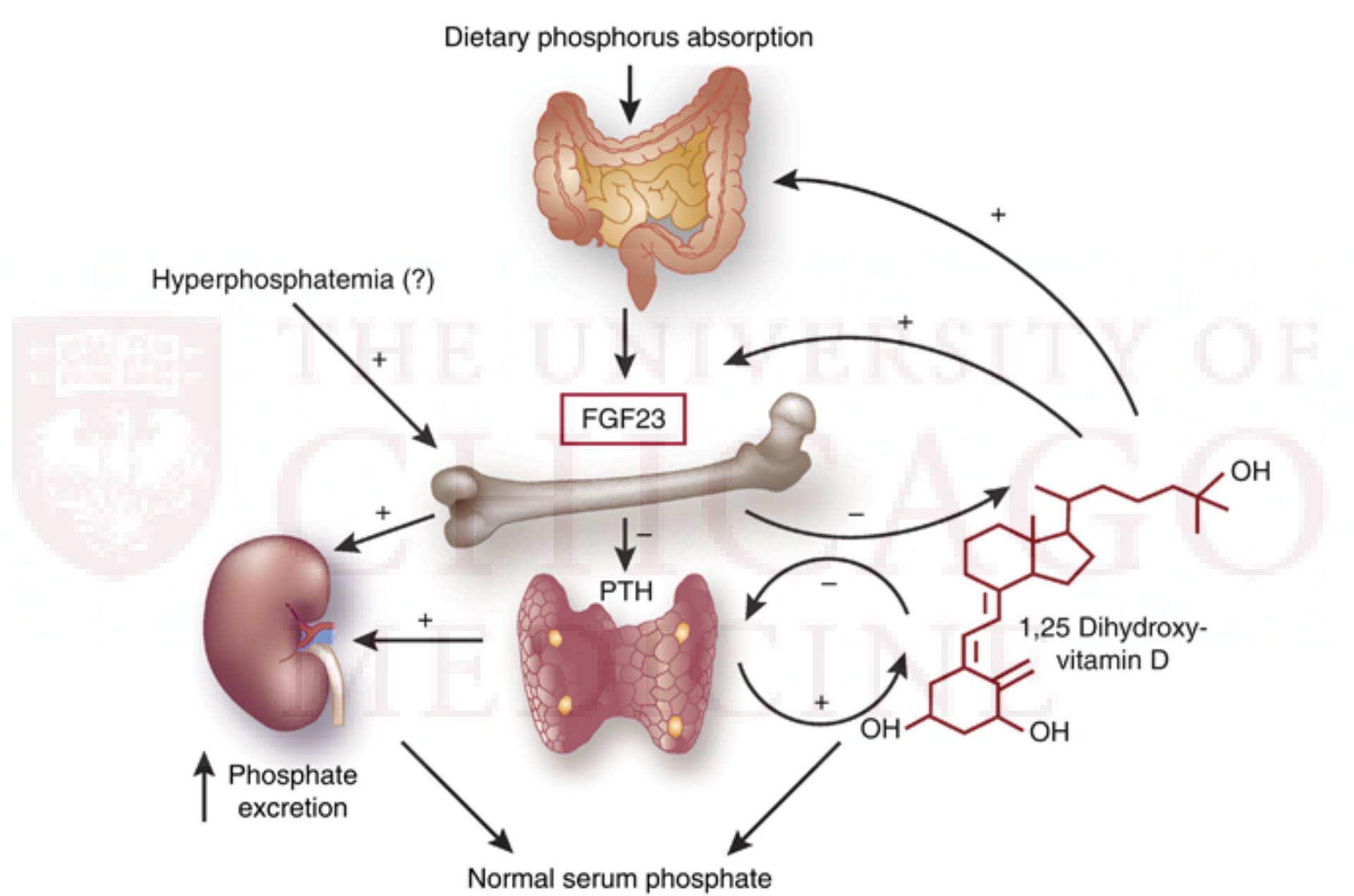
- His symptoms improved significantly with calcitriol and phosphate treatment

- What is a mechanism of hypophosphatemia in hypophosphatemic rickets?

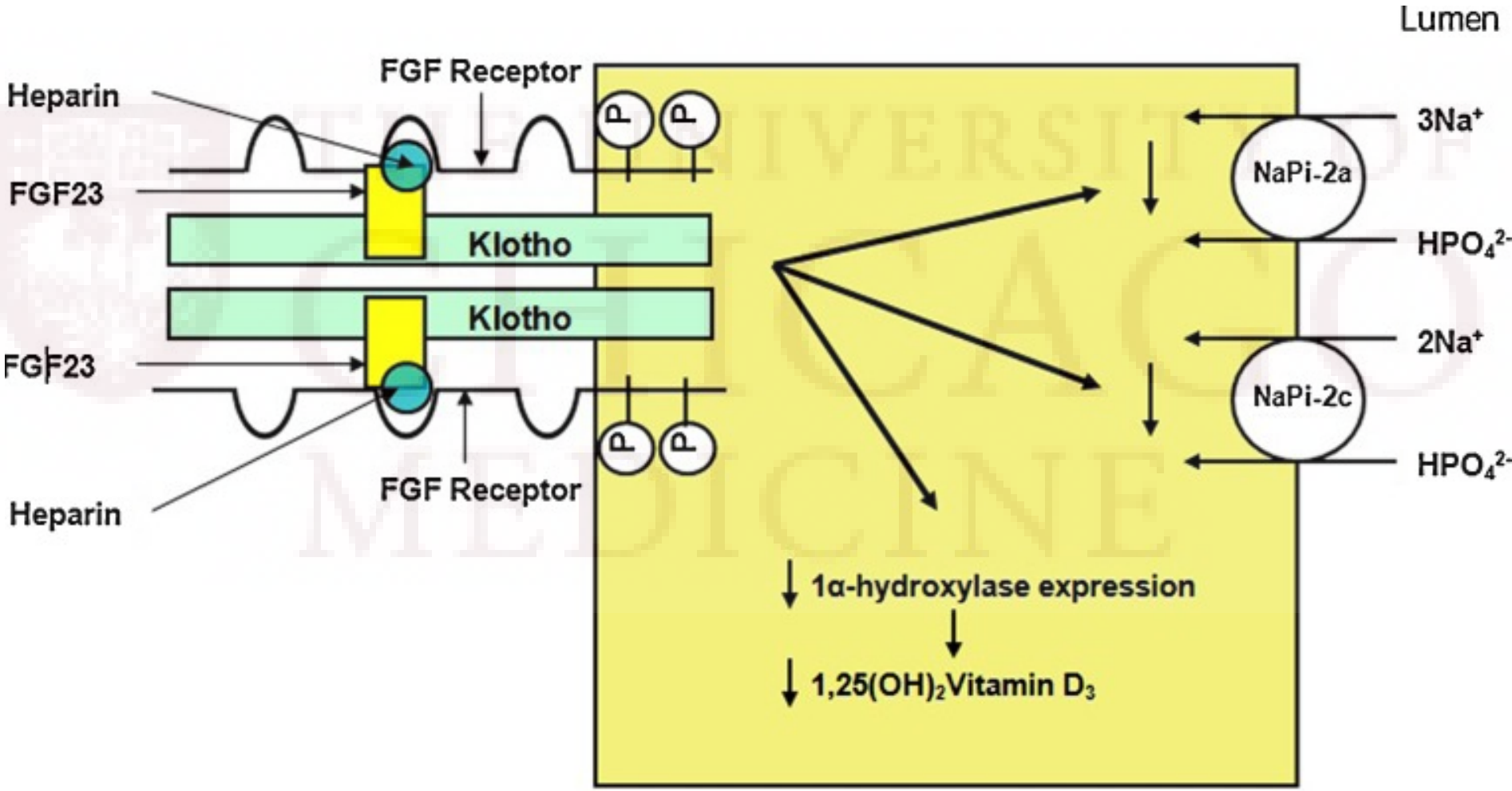
- How the patient should be managed?



Gattineni J, Baum M. Genetic disorders of phosphate regulation. Pediatr Nephrol. 2012 Sep;27(9):1477-87

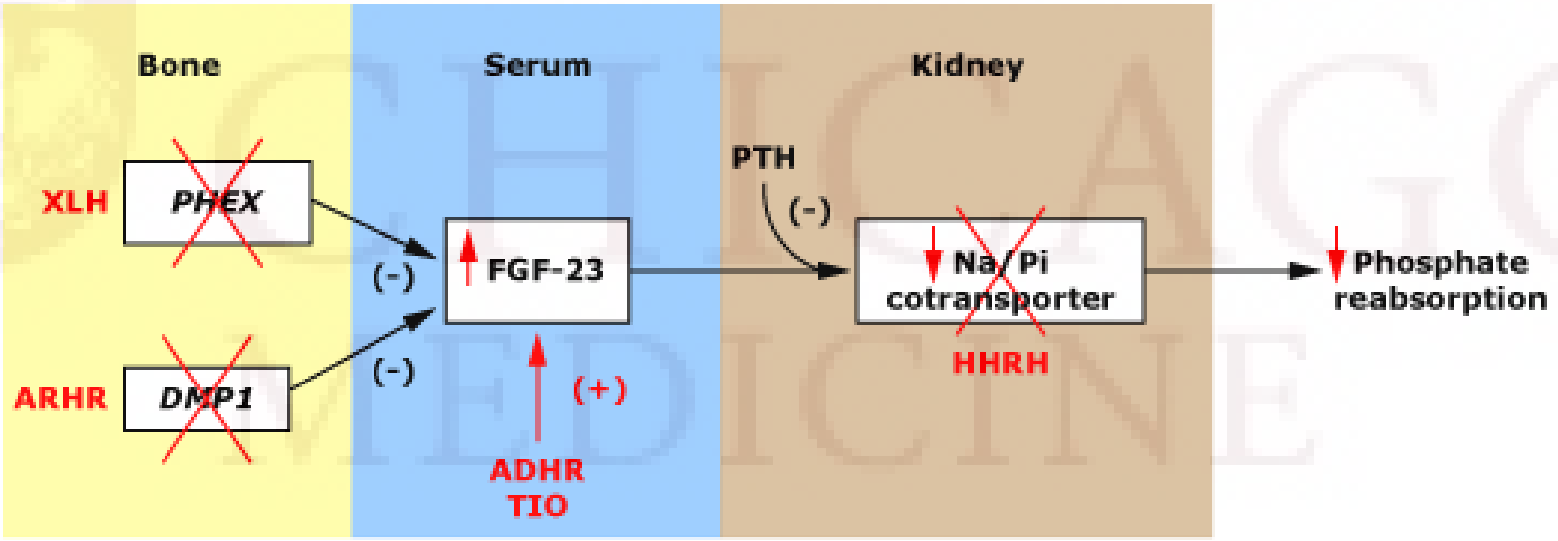


Isakova T, Gutiérrez OM, Wolf M. A blueprint for randomized trials targeting phosphorus metabolism in chronic kidney disease. Kidney Int. 2009 Oct;76(7):705-16

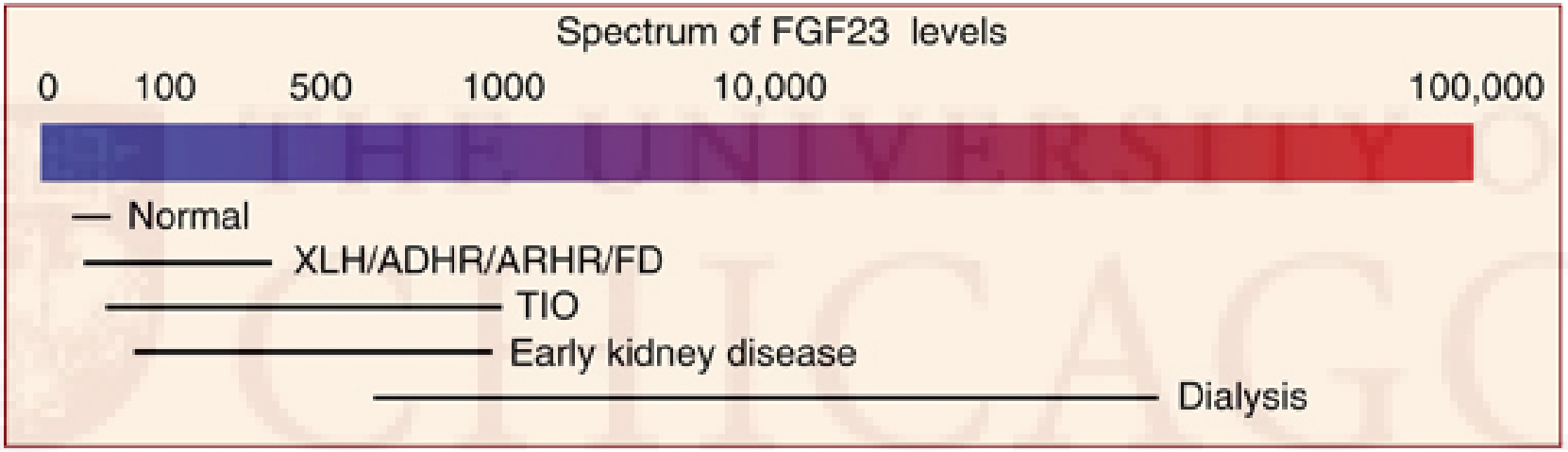


Gattineni J, Baum M. Genetic disorders of phosphate regulation. Pediatr Nephrol. 2012 Sep;27(9):1477-87

Pathways of renal phosphate wasting in hereditary hypophosphatemic rickets and tumor-induced osteomalacia



UptoDate



Metabolic characteristics of primary versus secondary syndromes of FGF23 excess

	FGF23	Serum Pi	Urinary Pi	1,25D	PTH
1° FGF23 Excess	↑	↓↓	↑	↔ / ↓	Variable
2° FGF23 Excess	↑↑↑	↔ / ↑	↑	↓↓	Variable / ↑↑

Isakova T, Gutiérrez OM, Wolf M. A blueprint for randomized trials targeting phosphorus metabolism in chronic kidney disease. Kidney Int. 2009 Oct;76(7):705-16

Treatment:

- Calcitriol is administered in two doses per day (10 to 20 ng/kg per dose)

- Phosphate is administered in a dose of 1 to 4 g/day in three to four divided doses

Complications from treatment:

- Described in patients with X-linked hypophosphatemic rickets

- **Hyperparathyroidism:** the administration of phosphate increases the plasma phosphate concentration, which reduces the plasma calcitriol concentration (by removing the hypophosphatemic stimulus to its synthesis). This causes secondary hyperparathyroidism.

- **Nephrocalcinosis:** linked to intermittent episodes of hypercalcemia and hypercalciuria. These can result from an excessive calcitriol dose or from noncompliance with oral phosphate supplementation.

Ways to overcome complications:

- dose of calcitriol should be reduced when hypercalcemia or hypercalciuria are present

- nonhypercalcemic analogues of calcitriol, such as 22-oxacalcitriol, may provide a similar increase in plasma phosphate without producing hypercalcemia or hypercalciuria (not analyzed in humans)

- Preliminary data suggests that adding cinacalcet to the regimen instead of calcitriol might prevent the development of hyperparathyroidism

Calcimimetics as an Adjuvant Treatment for Familial Hypophosphatemic Rickets

Uri S. Alon,* Rachel Levy-Olomucki,* Wayne V. Moore,† Jason Stubbs,‡ Shiguang Liu,‡ and L. Darryl Quarles‡

**Pediatric Nephrology, Bone and Mineral Disorders Clinic and †Pediatric Endocrinology, Children's Mercy Hospital, University of Missouri, Kansas City, Missouri; and ‡the Kidney Institute, University of Kansas Medical Center, Kansas University Medical Center, Kansas City, Kansas*

Design, Setting, Participants, and Measurements: Eight subjects with XLH were given a single oral dose of phosphate, followed the next day by combined treatment with phosphate and cinacalcet. Serum measurements of ionized calcium (Ca), phosphate, creatinine, intact PTH, 1,25(OH)$_2$D, FGF23, and tubular threshold for phosphate/glomerular filtration rate (TP/GFR) were assessed in response to short-term treatment with phosphate and cinacalcet and compared with long-term administration of phosphate and calcitriol.

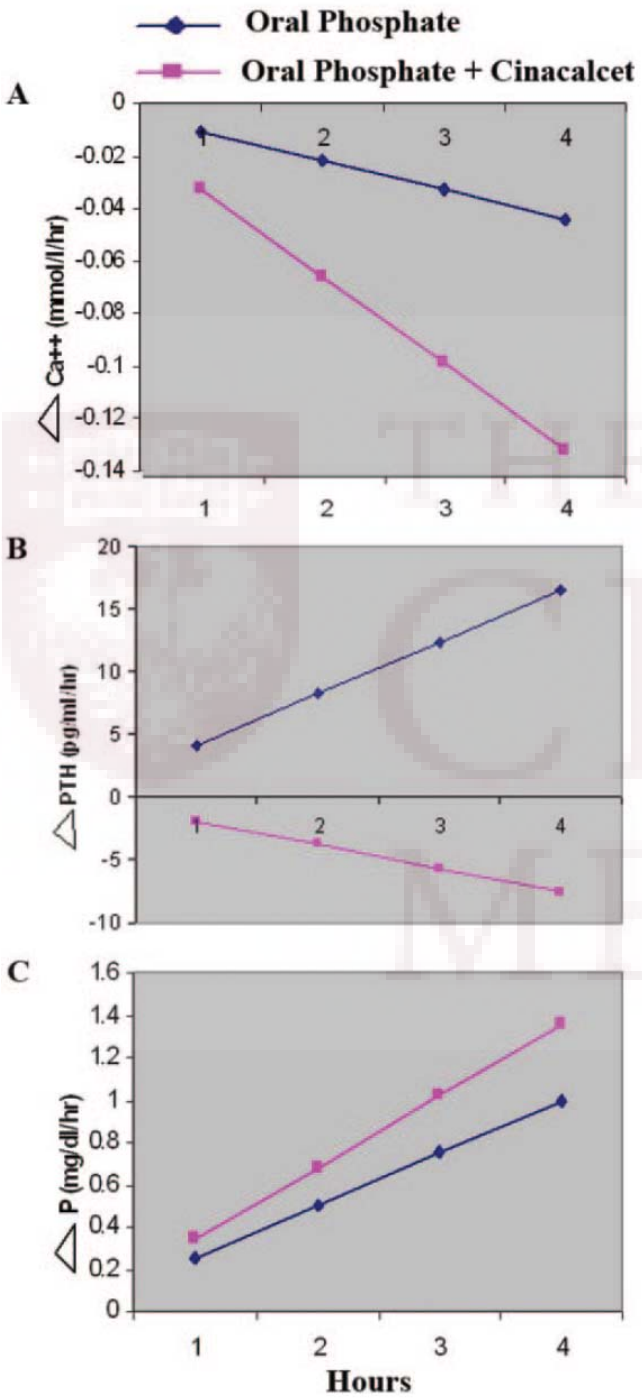


Table 1. Blood and urine biochemical and hormonal variables in 8 XLH subjects treated on day 1 with phosphate alone, on day 2 with phosphate + cinacalcet, and at follow-up after chronic treatment with phosphate + calcitriol

Treatment	Oral Phosphate: Day 1		Oral Phosphate + Cinacalcet: Day 2		Follow-up: Period E (oral phosphate + calcitriol)	Normal Range
	Period A: 0 h	Period B: 4 h	Period C: 0 h	Period D: 4 h		
Ca^{2+} (mmol/L)	1.28 ± 0.03	1.23 ± 0.04	1.26 ± 0.04	1.13 ± 0.06[c]	1.24 ± 0.07	1.13–1.37
Phosphate (mg/dl)	2.1 ± 0.4	3.1 ± 0.4[b]	2.2 ± 0.5	3.4 ± 0.3[e]	2.9 ± 0.6[b]	2.9–4.9
PTH (pg/ml)	36 ± 19	53 ± 13[c]	34 ± 6	23 ± 8[c]	33 ± 15	7–75
FGF23 (pg/ml)	147 ± 90	149 ± 67	192 ± 120[d]	221 ± 91[d]	247 ± 195[d]	9–53
1,25 vitamin D (pmol/L)	67 ± 35	75 ± 44	13 ± 21[d]	17 ± 25[d]	14 ± 6[d]	35–84
TP/GFR (mg/dl)	1.70 ± 0.38	1.81 ± 0.42	1.73 ± 0.36	2.48 ± 0.39[c]	1.86 ± 0.71	2.8–4.7
Ca/creatinine[a] (mg/mg)	0.12 ± 0.08	0.06 ± 0.04	0.13 ± 0.08	0.10 ± 0.08	0.14 ± 0.05	<0.20

[a]Measured in 6 subjects.
[b]$P < 0.05$ *versus* A, C.
[c]$P < 0.05$ *versus* all other groups.
[d]$P < 0.05$ *versus* A, B.
[e]$P < 0.05$ *versus* A, C, E ($P = 0.06$ *versus* B).

Alon US, Levy-Olomucki R, Moore WV, Stubbs J, Liu S, Quarles LD. Calcimimetics as an adjuvant treatment for familial hypophosphatemic rickets. Clin J Am Soc Nephrol. 2008 May;3(3):658-64

Take home points:

- Hypophosphatemic rickets is a rare disorder, related to phosphate wasting in kidneys
- The defect could be at a different level (bone – PHEX, DMP1, serum – FGF 23, kidney – Na-P co transporters)
- Phosphate and calcitriol are used for the treatment, phosphate and cinacalcet could be an alternative

References:

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