CKD Mineral Bone Disorder: Is FGF-23 the Answer?

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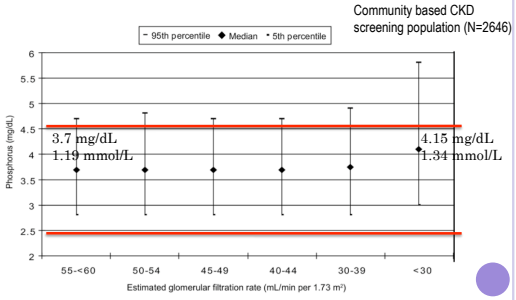
Outline

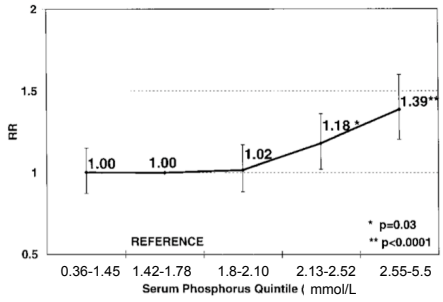
- Epidemiology of hyperphosphatemia and association with clinical outcomes
- Brief review of traditional pathogenesis of secondary hyperparathyroidism (SHPT) in chronic kidney disease (CKD)
- Role of fibroblast growth factor 23 (FGF-23) in SHPT
- New proposed pathogenesis of SHPT
- Potential clinical implications…..

Prevalence of Hyperphosphatemia by GFR



Am J Kid Dis 2008;51(S2):S56-S68.

Mortality Risk by Serum Phosphate Quintiles in Hemodialysis Patients



Block Am J Kid Dis 1998;31:607-17.

Serum Phosphate and Mortality in CKD Nondialysis

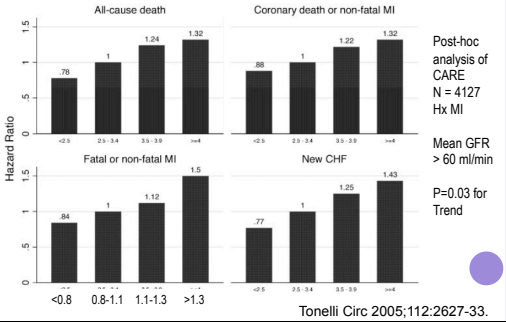
N=1203, CKD, mean eGFR 32 ml/min, P04 1.2 mmol/L

Quartiles: 12 month time-avg P04 (mmol/L)	All Cause Mortality HR (95% CI)	P
<1.02	1.0	
1.02-1.15	1.2 (0.8, 1.9)	0.4
1.16-1.34	1.2 (0.8, 1.8)	0.5
>1.34	**1.8 (1.1, 2.9)**	**0.01**

Survival analysis adjusted for age, gender, proteinuria, DM, Hgb, SBP, current smoking status, CVD, eGFR, vitamin D analog, phosphate binder

Eddington Clin J Am Soc Neph 2010:5:2251-7.

Clinical Outcomes by Baseline Serum Phosphate in Patients with CAD



Post-hoc analysis of CARE
N = 4127
Hx MI

Mean GFR > 60 ml/min

P=0.03 for Trend

Tonelli Circ 2005;112:2627-33.

Higher phosphate associated with increased CVD risk in the community

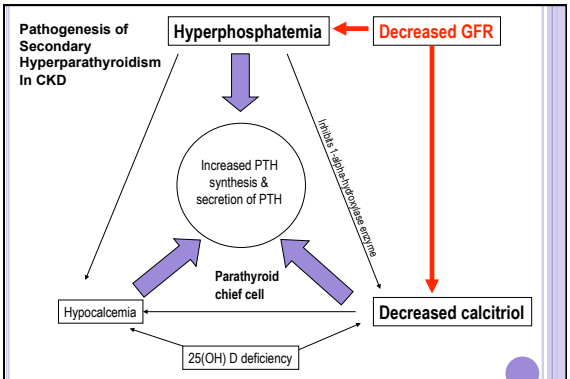
Phosphate Quartiles (mmol/L)	HR for CVD (95% CI)
Q1: 0.51-0.90	1 [reference]
Q2: 0.94-1.00	1.23 (0.95-1.59)
Q3: 1.03-1.10	1.27 (0.97-1.67)
Q4: 1.13-2.00	1.55 (1.16-2.07)
P value for trend	0.004

Cox proportional hazards model examining relations of P04 and Ca levels to incidence of CVD

N=3368 Framingham Offspring, free of CVD and CKD, 16 yrs f/u

Multivariable model adjusted for age, sex, BMI, DM, SBP, smoking, alcohol, TC/HDL ratio, Hgb, serum albumin, eGFR, proteinuria, CRP

Dhingra Arch Intern Med 2007;167:879-85.



Adapted from Qunibi WY. Renal osteodystrophy. In: Henrich WL, ed. *Principles and Practiceof Dialysis*. 4th edition. Philadelphia, PA; Lippincott Williams & Wilkins; 2009;431 (Fig 25-3)

Prevalence of abnormalities by GFR

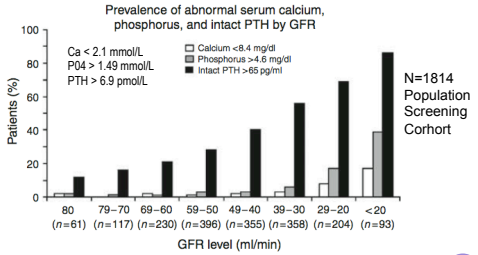
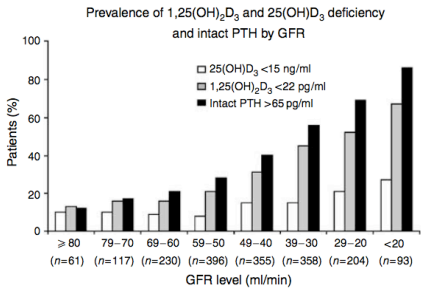


Figure 4 | The prevalence of HPTH, hypocalcemia, and hyperphosphatemia by eGFR levels at 10 ml/min intervals.

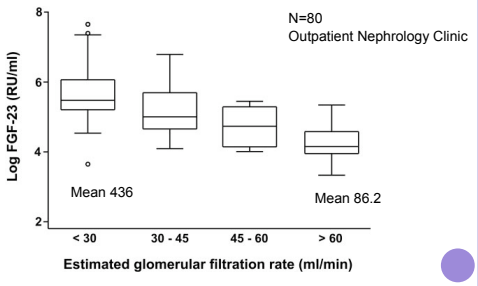
Levin A Kid Int 2007;71:31-8.

1,25 dihydroxyvitamin D levels decrease early in CKD



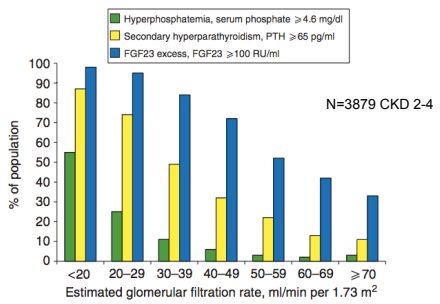
Levin A Kid Int 2007;71:31-8.

FGF-23 Levels Increase with GFR Decline



Gutierrez J Am Soc Neph 2005;16:2205-15.

FGF-23 increases early in CKD



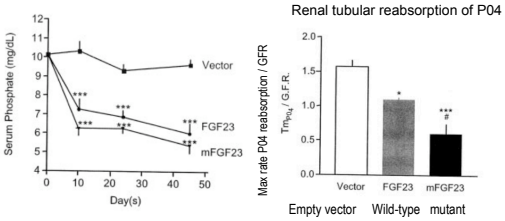
Isakova Kidney Int 2011;79:1370-8.

What the FGF-23?

- Fibroblast growth factor-23 (FGF-23)
  - Endocrine hormone; 251 amino acid protein
  - Synthesized & secreted by bone cells (mostly osteoblasts)
  - Discovered in rare disorders associated with urinary phosphate wasting:
    - Oncogenic osteomalacia – overproduction of FGF-23
    - Autosomal dominant hypophosphatemic rickets – mutations of FGF-23 resists cleavage, enhancing/prolonging activity
  - Animal studies:
    - FGF23 induces phosphaturia
    - FGF23 inhibits calcitriol synthesis

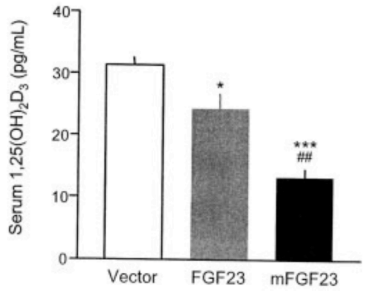
Jonsson N Engl J Med 2003;348:1656-63.

Animal models: FGF23 promotes phosphaturia



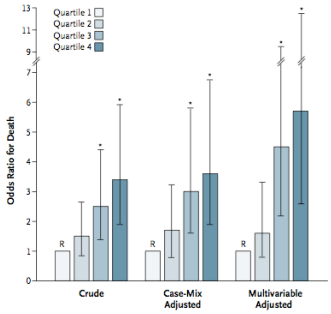
Bai J Biol Chem 2003;278:9843-9.

Animal models: FGF-23 reduces calcitriol



Bai J Biol Chem 2003;278:9843-9.

Mortality Associates with FGF-23 in Incident Hemodialysis Patients



Cohort of 10,044 incident hemodialysis patients

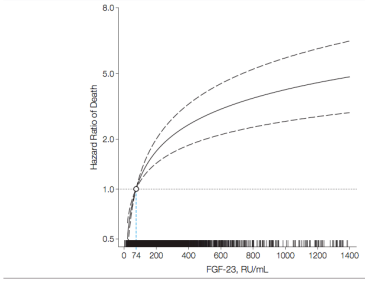
Nested case control study of 200 died and 200 survived in first year.

OR for Death (mulitvariable adjusted):
Q2: 1.6 (0.8-3.3)
Q3: 4.5 (2.2-9.4)
Q4: 5.7 (2.6-12.6)

Gutierrez NEJM 2008;359:584-92.

Mortality Associates with FGF-23 in Early CKD

Figure 1. Multivariable-Adjusted Hazard Function for Death According to Measured (Untransformed) Levels of Fibroblast Growth Factor 23



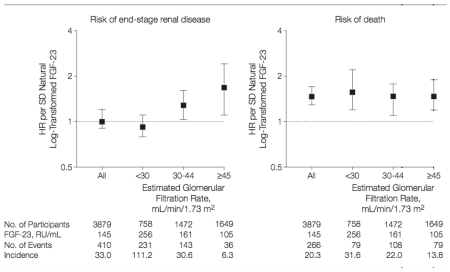
N=3879
CKD stage 2-4

Mortality risk increased by quartile of FGF-23
Q2: HR 1.3 (95% CI 0.8-2.2)
Q3: HR 2.0 (95% CI 1.2-3.3)
Q4: HR 3.0 (95% CI 1.8-5.1)

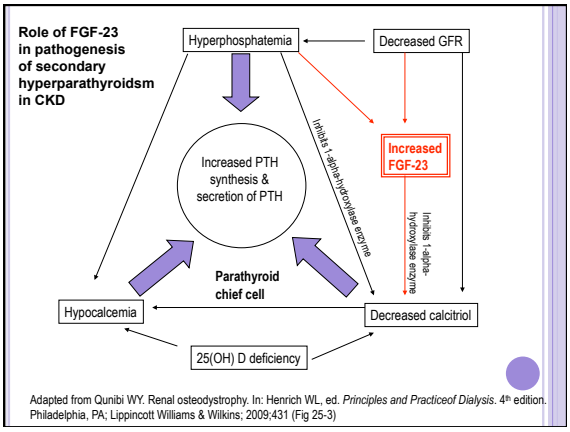
Isakova JAMA 2011;305:2432-9.

FGF-23 levels & risk of ESRD and death by baseline GFR

Figure 3. Fibroblast Growth Factor 23 Levels and Risks of End-Stage Renal Disease and Death by Baseline Kidney Function

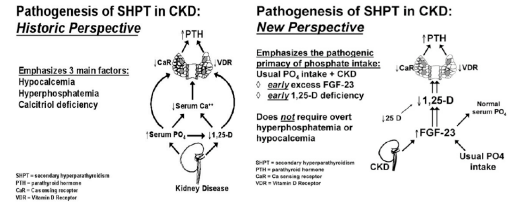


Isakova JAMA 2011;305:2432-9.



Adapted from Qunibi WY. Renal osteodystrophy. In: Henrich WL, ed. *Principles and Practiceof Dialysis*. 4th edition. Philadelphia, PA; Lippincott Williams & Wilkins; 2009;431 (Fig 25-3)

Pathogenesis of SHPT - New Paradigm!



Wahl & Wolf Adv Exp Med Biol 2012;728:107-25.

Potential Clinical Implications....

Can we decrease FGF-23 with therapeutic interventions?

Can diet reduce FGF-23?

- Crossover trial, N=9, eGFR 32 ml/min
- Comparison of vegetarian and meat diets with equivalent nutrients (P04: 800 mg/d)

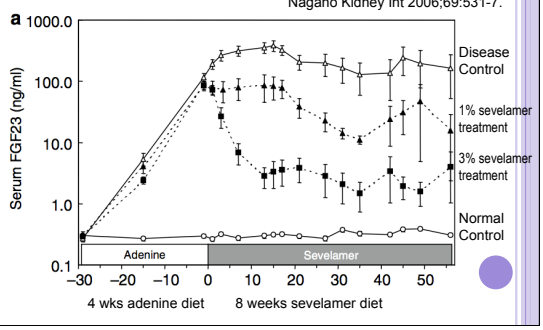
Plasma levels	Before Meat diet	1 wk After Meat diet	Before Vege diet	1 wk After Vege diet	P (paired t test)
P04 (mg/dL)	3.5 +/- 0.6 (1.13 mmol/L)	3.7 +/- 0.6 (1.19 mmol/L)	3.5 +/- 0.6 (1.13 mmol/L)	3.2 +/- 0.5 (1.03 mmol/L)	0.02
Intact PTH (pg/ml)	58 +/- 31	46 +/- 29	58 +/- 39	56 +/- 30	0.002
FGF-23 (pg/ml)	72 +/- 39	101 +/- 83	84 +/- 65	61 +/- 35	0.008

- NS: plasma Ca, CrCl, urine 24-hr Ca or P04 excretion

Moe SM Clin J Am Soc Neph 2011:6;257-64.

Rat model: Effect of sevelamer on FGF-23

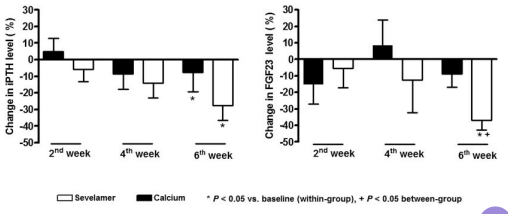
Nagano Kidney Int 2006;69:531-7.



Sevelamer vs Ca Acetate Effect on FGF-23 & PTH

N=40, RCT, open-label
CKD stage 3-4, 6 week titration
Calcium acetate 1.32 g/d, doubled q2wk until 5.28 g/d (8 tabs/d)
Sevelamer HCl 1.6 g/d, doubled q2wk until 6.4 g/d (8 tabs/d)

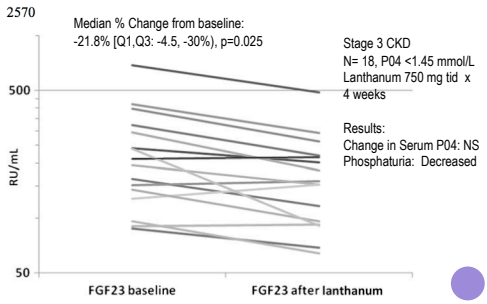
Baseline: CrCl 35 ml/min, P04 1.14 mmol/L
PTH 101 pg/ml, Ca 2.32 mmol/L



Study funded by Genzyme

Oliveira CJASN 2010;5:286-91.

Lanthanum reduces FGF-23 in CKD 3



Gonzalez-Parra Nephrol Dial Transplant 2011;26:2567-71.

Calcium acetate vs Sevelemer Effect on FGF-23 & Vascular Function

- N=100, RCT, open-label, Stage 4 CKD, hyper-P04
- Sevelamer (1.6 g TID) vs calcium acetate (1 g TID) x 8 wks titrated to P04 < 1.78 mmol/L
- Primary outcome: flow mediated vasodilatation
  - Sevelamer – increase from 6.1 to 7.1%, p<0.001
  - Ca acetate – no change (6 vs 6%)
- Changes in FGF-23 levels
  - -27.1% [-33.2 to -8.8%, p<0.001] for sevelamaer group
  - 3.5% [-8.4 to 12.1%] for Ca acetate group
- Limitations: unblinded, can not establish mechanism of effect, surrogate outcome, low Ca acetate dose, baseline P04 2.48 mmol/L

Yilmaz AJKD 2012;59:177-85.

Summary

- FGF-23 is a key regulator of phosphate homeostasis and increases early in CKD, before hyperphosphatemia is evident
- FGF-23 is associated with increased mortality and is an independent predictor of progression to ESRD, particularly in early CKD
- Further studies are needed to determine whether early strategies to reduce phosphate burden in patients with normal phosphate levels will decrease FGF-23 and impact hard clinical outcomes