Hyperphosphatemia, How to treat?

INTRODUCTION

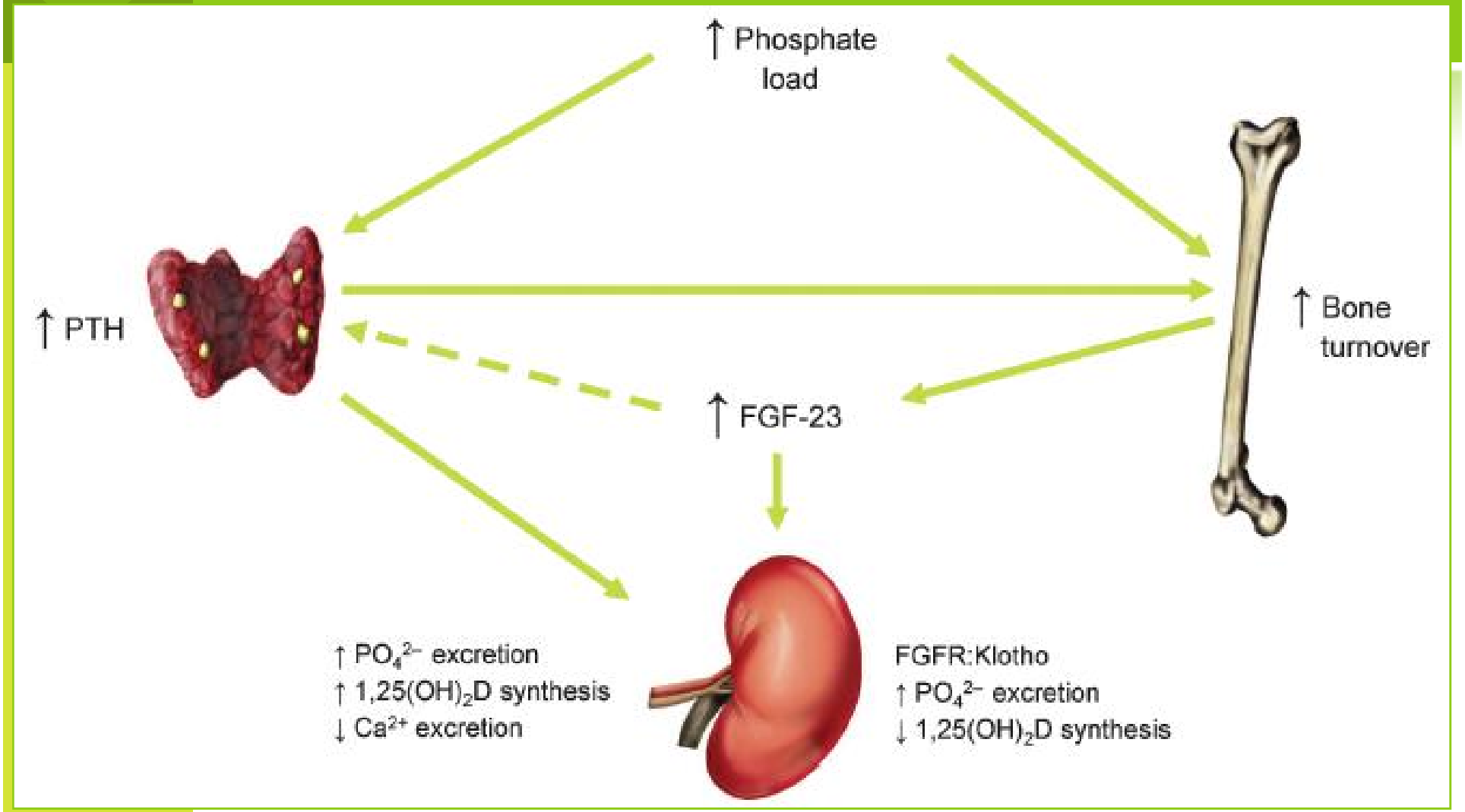
- Phosphate retention begins early in renal disease, due to the reduction in the filtered phosphate load.
- Phosphate retention is closely related to
  1. Cardiovascular disease risk in CKD,
  2. Increased FGF-23 levels
  3. Secondary hyperparathyroidism

FGF-23 APPEARS TO BE THE INITIAL HORMONAL ABNORMALITY

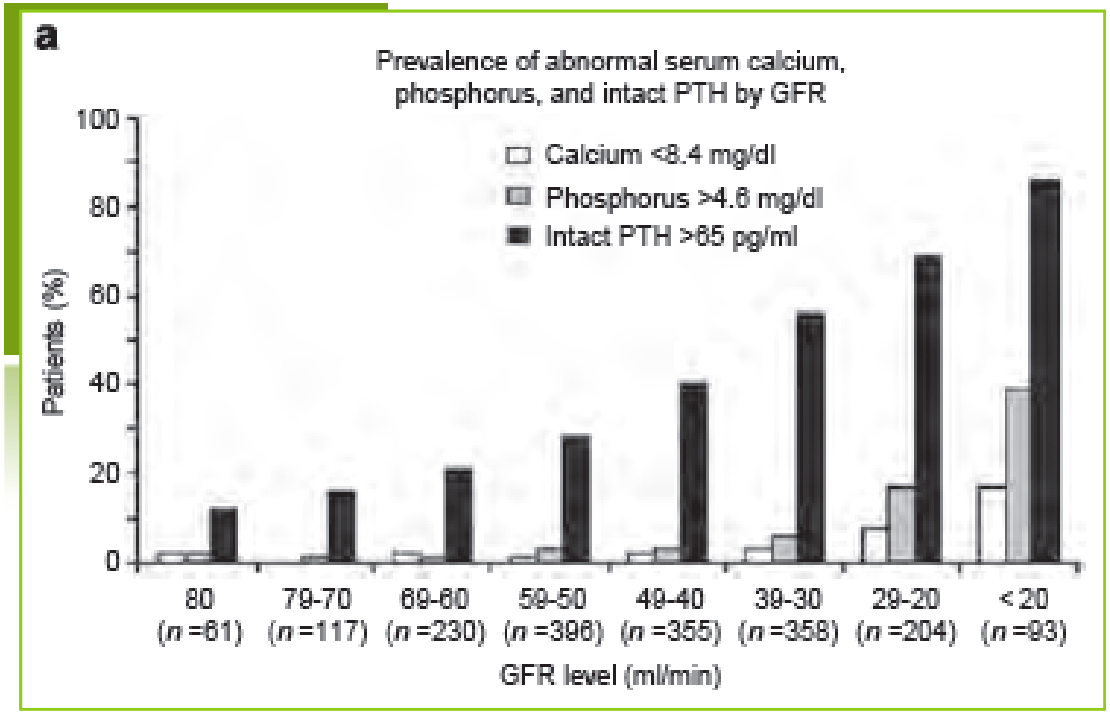
- Increased FGF-23 leads to:
  1. Increased urinary phosphate excretion
  2. Suppression of $1,25(OH)_2D$.
- PTH increases in response to reductions in $1,25(OH)_2D$.
- PTH can correct both the hypocalcemia and the hyperphosphatemia by increasing bone turnover & Ca- P release from bone and enhancing urinary phosphate excretion.

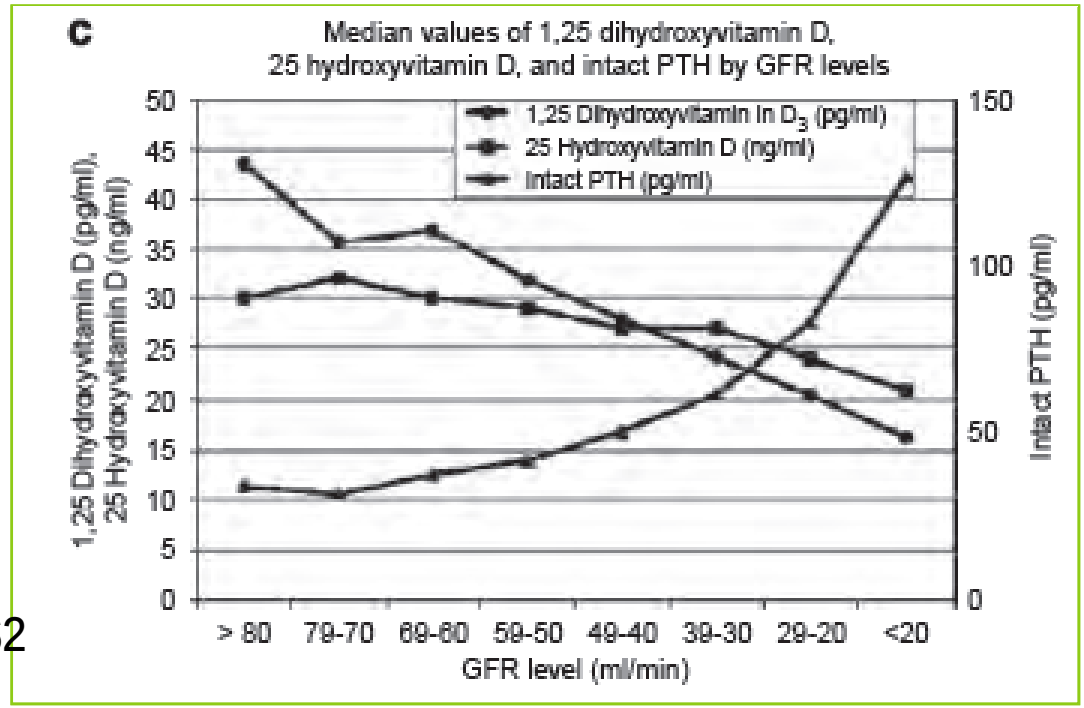
FGF-23

- FGF-23 is also important in the renal adaptation to maintain phosphate excretion.
- The fraction of the filtered phosphate that is reabsorbed, progressively reduces from the normal value of 80 -95% to as low as 15% in advanced renal failure
- Phosphate balance and a normal serum phosphate concentration are generally maintained until GFR falls below 25 -40 mL/min, at the price of elevated FGF-23 and hyperparathyroidism.



Effect of dietary phosphorus load on phosphorus metabolism in the body.





KDIGO 2009KI(2009) 76 (Suppl 113), S1–S2

Treatment Strategies: Dietary Phosphate Restriction

Dietary Phosphate Restriction

- Fewer than 50% of patients ESRD meet target levels for serum phosphorus.

Young EW AJKD 2004

Target Levels: K/DOQI, Emerging Questions

Patel TV. Semin Nephrol.2009 March;29(2):105–112.

	Ca (mg/dL) ▲	P (mg/dL)	PTH pmol/L	Ca Intake	Ca´P
CKD ND	Normal Lab Range	2.7- 4.6 (0.87-1.49 mmol/L)	<70 stage 3 <110 stage 4	1.4- 2 gr/d@	<55•
CKD 5D	8.4 to 9.5 (<10.2)* (2.1-2.37 mmol/L)	3.5-5.5** (1.13-1.78 mmol/L)	150-300♪	1.4- 2 gr/d@	<55•
*Values up to 10.5 have been shown not to increase mortality.					
**Mortality may not be increased with serum P 3.0-7.0					
@It is reasonable to keep Ca intake below 1.4 gr/day					
▲Measurment of iCa is suggested by KDIGO and European studies.					
♪Since iPTH>200 has been associated with CVD outcome, it is important to treat it with activated vitamin D aggressively					
•All-cause mortality did not differ for the Ca x P range of 40–75mg^2/dL^2					

*/**/♪/•/Kalantar-Zadeh K. Kidney Int 2006;70:771. @Mehrorta R. Kidney Int 2005;68:1258
▲Gauci C. J Am Soc Nephrol 2008;19:1592–1598.

Dietary Phosphate Restriction

- Dietary phosphate restriction may reduce the serum concentration of phosphate, FGF-23, and PTH, till the relatively late stages of CKD, although not usually to normal.

Noori N. IJKD 2010;4:89-100

Organic & Inorganic Dietary P & Its Management in CKD

- The main food sources of phosphorus are the protein food groups of meat, poultry, fish, eggs, & dairy products.
- Plants: some plant seeds, beans, peas, cereals, nuts, legumes, cocoa,
- A large whole egg contains 6 g of protein and 86 mg of P, whereas egg white from 1 large egg (3.6 g protein) contains 5 mg of P, indicating that the bulk of egg phosphorus is in the egg yolk.
- Poultry contain less P than red meat and fish

Noori N.IJKD 2010;4:89-100

Organic & Inorganic Dietary P & Its Management in CKD

- Phosphorus in plants, especially in beans, peas, cereals, and nuts, is mostly in the storage form of phytic acid or phytate, with a low absorption rate.
- Digestibility of P from animal-derived foods is higher than that of plant-based proteins.
- >90% of inorganic P from processed food may be as opposed to only 40-60% of the organic P present in natural foods

Noori N.IJKD 2010;4:89-100

A LARGE FRACTION OF DIALYZED PATIENTS HAVE EITHER OVERT OR BORDERLINE MALNUTRITION

- In dialysis patients protein supplementation rather than protein restriction is the goal.
- Phosphate restriction should primarily include processed foods and colas and NOT high biologic value foods such as meat and eggs.
- The average daily dietary intake of P is about 1550 mg for males and 1000 mg for females.
- Approximately 900 mg phosphorus per day is relatively acceptable.

A LARGE FRACTION OF DIALYZED PATIENTS HAVE EITHER OVERT OR BORDERLINE MALNUTRITION

- Unnecessary dietary phosphate:
  - phosphorus-containing food additives,
  - dairy products,
  - certain vegetables,
  - many processed foods, and colas
- Patients should restrict these foods while increasing the intake of high biologic value sources of protein such as meat and eggs.

PHARMACOLOGIC THERAPY

Sevelamer hydrochloride (Renagel) Sevelamer Carbonate (renvela)

- Clinical studies with this drug are mainly restricted to patients undergoing hemodialysis.
- Sevelamer is well tolerated in dialysis population and effective in reducing both serum P and Ca-P product.
- Randomized, double-blind, placebo-controlled phase II study in 36 patients (12 in the placebo group and 24 in the active group), with an 8-week follow-up period, showed that sevelamer was equivalent to calcium-based binders in reducing phosphorus levels.

Chertow GM. Am J Kidney Dis. 1997;29(1):66-71.

- An open-label, randomized, crossover phase II study, compared sevelamer with calcium acetate in 84 HD patients with serum P> 6 mg/dL. A
- Both drugs reduced P by 2 mg/dL ($p < 0.0001$).
  - 5% of patients treated with sevelamer had at least one episode of serum calcium > 11 mg/dL.
  - 22% of patients in the group receiving calcium acetate ($p < 0.05$).
- PTH levels decreased in both groups, most significantly in the group treated with calcium acetate.
- Values for the Ca-P decreased in both groups, with no statistical difference ($p = 0.66$).

Bleyer AJ. Am J Kidney Dis. 1999;33(4):694-701.

- Although conventional dosing of sevelamer is effective, compliance with the requirement for thrice daily dosing with any phosphate binder can be problematic.

- A small crossover study found that once-daily sevelamer was as effective as thrice-daily dosing of sevelamer in controlling serum P, Ca, CaxP product, serum albumin, and serum lipid levels.

Fischer D. Am J Kidney Dis. 2006;48(3):437

LANTHANUM CARBONATE (FOSRENOL)

- Because of high cost its use is limited to patients with hypercalcemia, or as an adjunct to a regimen supplying a maximum dose of 1500 mg of elemental calcium from calcium-based phosphate binders.
- It reduces pill burden (pills of 500, 750 and 1000 mg, with dosage of 1500 to 3000 mgr/day (max: 4500)
- Fosrenol is the largest of all pills filled in community pharmacies. Sometimes patients forget that fosrenol is not swallowed whole, but instead should be chewed. This has led to severe choking.
- Appears to be associated with a lower incidence of hypercalcemia and decreased PTH levels versus calcium-containing phosphate binders.
- Myalgia, muscular cramping, and peripheral edema

- A randomized study on 800 patients who received either lanthanum (750-3000 mg) or calcium carbonate (1500-9000 mg).
- Around 65% of patients in each group achieved phosphate control, but in the calcium carbonate group this was at the expense of significant hypercalcemia (20.2% of patients vs. 0.4%).
- Consequently, calcium x phosphate product tended to be better controlled in the lanthanum group.

Hutchison AJ, Nephron Clin Pract. 2005;100(1):c8-19.

CALCIUM CONTAINING DRUGS

- They bind P in the intestinal lumen, & reduce its absorption.
- The main problem with these drugs is the transient episodes of hypercalcemia, requiring reduction of the dose of vitamin D analogues and adjustment of the calcium concentration of the dialysis solution.
- Ca concentration in HD or PD should be 2.5 meq/L (1.25 mmol/L) (K/DOQI 2003) or 2.5-3.0 (KDOGO 2009)

- Withdrawal or dose adjustment of vitamin D analogues) or reduction in dialysate calcium levels (maximum calcium concentration of 2.5-3.0 mEq/L) may be considered in patients with persistently high Ca and P levels.

- CaCO3 dissolves only at an acid pH and many patients with advanced renal failure have achlorhydria or are taking H2-blockers.
- Calcium acetate, on the other hand, is soluble in both acid and alkaline environments and is a more efficient phosphate binder.
- It can be used in half dose of CaCO3.
- However the incidence of hypercalcemia is the same with half dose of Ca-Acetate compared to CaCo3

Delmez JA. J Am Soc Nephrol. 1992;3(1):96
Morinière P. Nephron. 1992;60(1):6

AL(OH)3

- Patients showing high P levels despite high doses of calcium-based binders may receive aluminum hydroxide for a limited period of time (2-4 weeks) in order to prevent hypercalcemia.
- Aluminum hydroxide is a binder more powerful than calcium-based agents, but its use has been avoided or, if used, limited because of toxic effects reported on the central nervous system, bone, and hematopoietic tissue.

NICOTINAMIDE

- Nicotinamide, a metabolite of nicotinic acid (niacin, vitamin B3), inhibits the Na/Pi co-transport in the GI tract and kidneys and may be effective in lowering P levels in dialysis patients by reducing GI tract P absorption.

POLYNUCLEAR IRON (III)-OXYHYDROXIDE PHOSPHATE (PA21)

- 154 participants were randomized to PA21 at dosages of 1.25, 5.0, 7.5, 10.0, or 12.5 g/d or sevelamer-HCl 4.8 g/d for 6 weeks
- All groups except PA21 1.25 g/d showed a significant decrease in serum P.
- The 5 g/d and 7.5 g/d dosages showed similar efficacy to 4.8 g/d of sevelamer-HCl.
- The most frequent adverse events were hypophosphatemia (18.0%) and discolored feces (11.7%) for the PA21 dose groups, and diarrhea, hypophosphatemia, and hypotension (each 11.5%) for sevelamer-HCl.
- The adverse events rate was similar for PA21 and sevelamer-HCl.

Wüthrich RP .Clin J Am Soc Nephrol. 2013 Feb;8(2):280-9.

Drug Preparations & Dosage

	Tab. (Suspension)	P level	dosage
Al(OH)3	300 mg (320 mg/5 ml)	Usually P >7 mg/dl	300-600 mg tid
CaCO3	500 mg		500 mg tid (max 2 g)
SevelamerHCl	800 mg	5.5-7.4 mg/dL 7.5-9.0 mg/dL ≥9.0 mg/dL	800 mg 3 tid 1200-1600 mg 3 tid 1600 mg 3 tid (Max:7200 mg/day)

DIALYSIS

- The average standard dialysis removes about 900 mg of P.
- Phosphate removal during dialysis is limited largely due to the intracellular location of most inorganic phosphorous.
- Full dialyzer clearance is effective in only the initial phase of the dialysis treatment.
- After this initial phase, the transfer rate for phosphate from the intracellular space to the plasma becomes the rate-limiting step for phosphate transport.
- However there several studies have shown that short daily hemodialysis improves phosphate balance.

Pohlmeier R .Kidney Int Suppl. 2001 Feb;78:S190-4

FACTORS WHICH INFLUENCE P REMOVAL IN HD

P. GALLAR, NEFROLOGÍA. 27 (1).2007

- 108 HD patients, 62% men, 38% women aged 21-82 years
- There was a good correlation between P removal and Serum phosphate levels (p = 0.01) , Blood V (L) that passed the dialyzer in each session (r = 0.01) and AV fistula as vascular access (p = 0.05).
- No correlation was found between P removal and membrane surface, KT/V, the dialysate flux, the ultra filtration or treatment duration.
- Phosphate removal was 640 ± 180 mg/session with low-flux membrane and 700 ± 170 mg/session with high-flux membrane (p
- On-line HDF technique did not increased the MPO4.
- The on-line technique with the new dialyzer (Fresenius Fx100), increased the phosphate removal to 759 ± 199 mg/session (p = 0.057).
- On multivariate analysis, plasma phosphate and the volume of blood that passed the dialyzer in each session predicted phosphate removal.

THERAPEUTIC STRATEGIES

- Consider patients with CKD stages 3–5D with known vascular/valvular calcification to be at the highest cardiovascular risk
- In CKD stages 3–5D & hyperphosphatemia:

– Restrict the dose of Ca-based phosphate binders and/or the dose of calcitriol or vitamin D analog in the presence of persistent or recurrent hypercalcemia .

– Restrict the dose of calcium-based phosphate binders in the presence of arterial calcification (2C) and/or adynamic bone disease (2C) and/or if serum PTH levels are persistently low.

- In patients with CKD stages 3–5D, avoid the long-term use of aluminum-containing phosphate binders and, in patients with CKD stage 5D, avoiding dialysate aluminum contamination to prevent aluminum intoxication
- In patients with CKD stages 3-5D, limit dietary phosphate intake in the treatment of hyperphosphatemia alone or in combination with other treatments.
- In patients with CKD stage 5D, increase dialytic phosphate removal in the treatment of persistent hyperphosphatemia.