Fisiopatologia del metabolismo minerale: ruoli e interazioni di Calcio, Fosforo e PTH

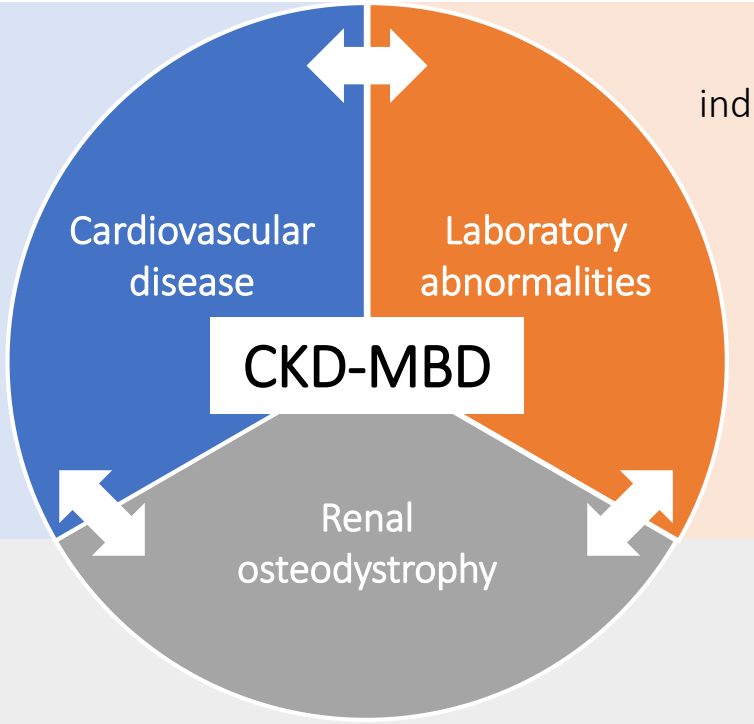
Maurizio Gallieni

What is CKD-MBD?

CKD-MBD represents three closely related disease conditions

Cardiovascular disease represents accelerated arteriosclerosis, left ventricular hypertrophy and a variety of additional pathologies in the vasculature and heart of patients with CKD

Laboratory abnormalities indicative of disturbed bone and mineral metabolism

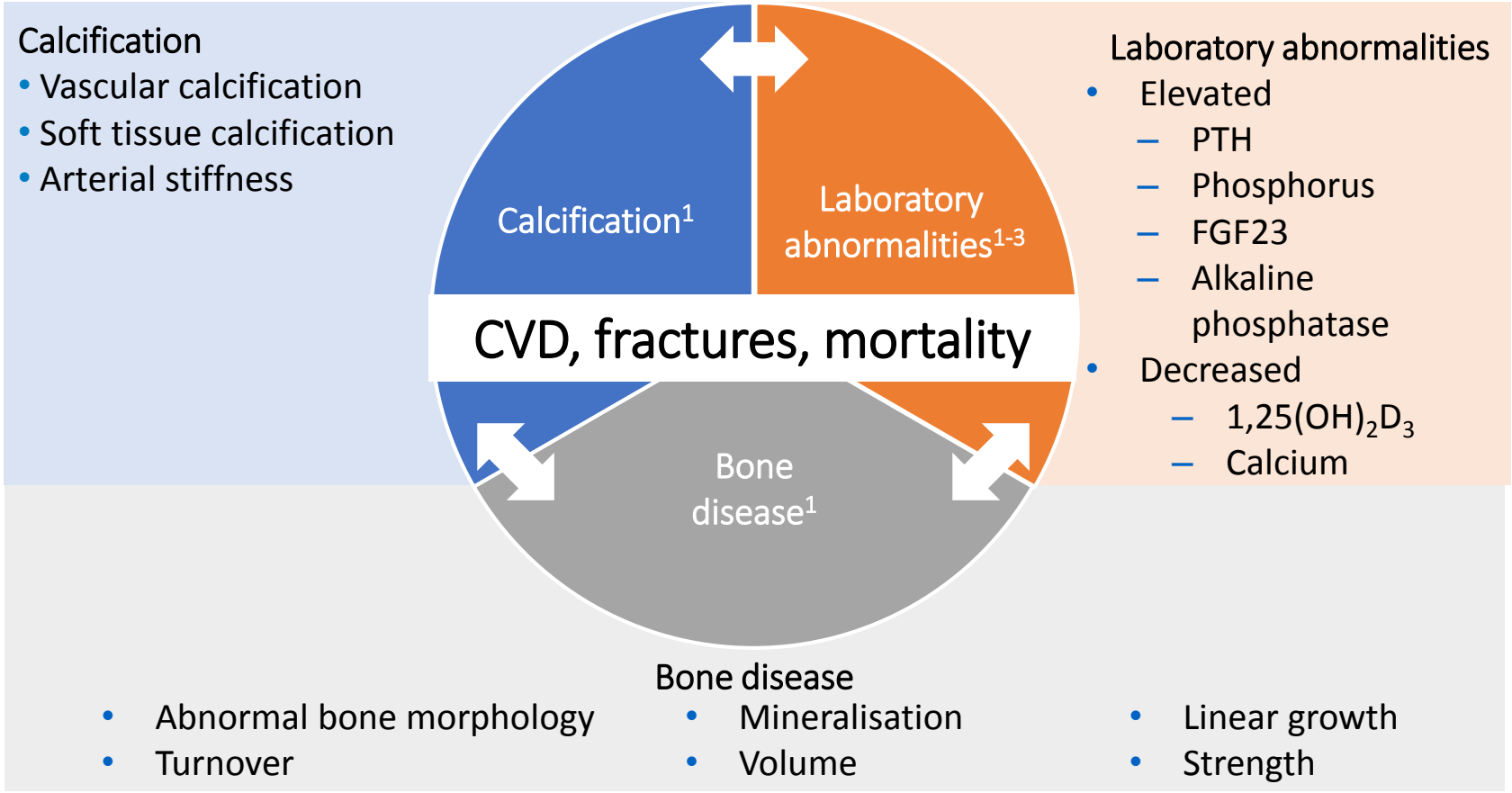


Renal osteodystrophy encompasses the variety of bone lesion subtypes occurring in CKD

Adapted from: Cozzolino M, et al. Nephrol Dial Transplant 2014;29:1815–1820.

CKD-MBD: A multifactorial progressive disorder

CKD-MBD is the expression of three closely related disease conditions

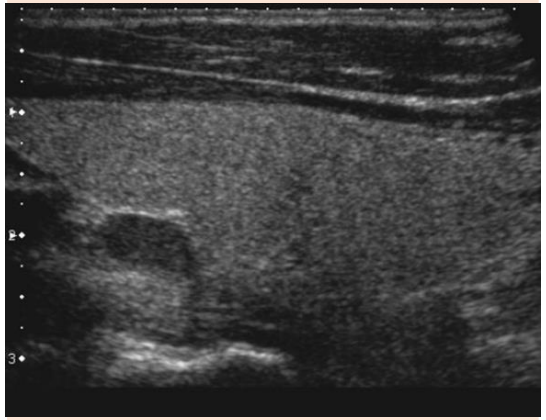


Adapted from: Kidney Disease: Improving Global Outcomes (KDIGO) CKD–MBD Work Group. Kidney Int 2009;76(Suppl 113):S1–130.
1. Moe S, et al. Kidney Int 2006;69:1945–1953; 2. National Kidney Foundation. Am J Kidney Dis 2003;42(suppl 3):S1–S201;
3. Urena Torres P, et al. Kidney Int 2008;73:102–107

CKD-MBD: Disease conditions

LABORATORY ABNORMALITIES

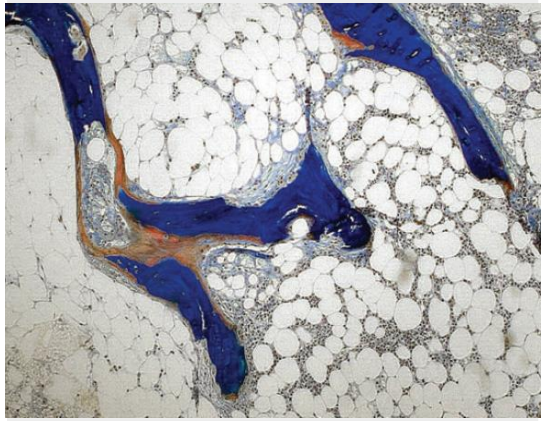
Laboratory abnormalities of calcium, inorganic phosphorus, PTH or vitamin D



Thyroid gland ultrasonography showing the right upper parathyroid gland in a dialysis patient with uncontrolled hyperparathyroidism

BONE DISEASE

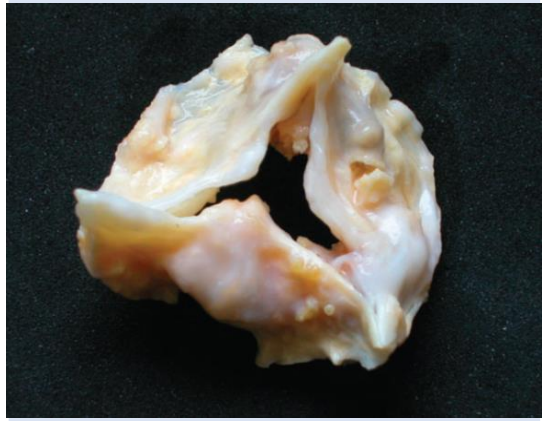
Bone abnormalities in turnover, mineralisation, volume, linear growth or strength



Bone histology: mixed uraemic osteodystrophy characterised by high cellular activity with osteoclastic giant cells in resorption lacunae, osteoid accumulation and peri-trabecular fibrosis*

CALCIFICATION

Calcification of the vasculature or other soft tissues

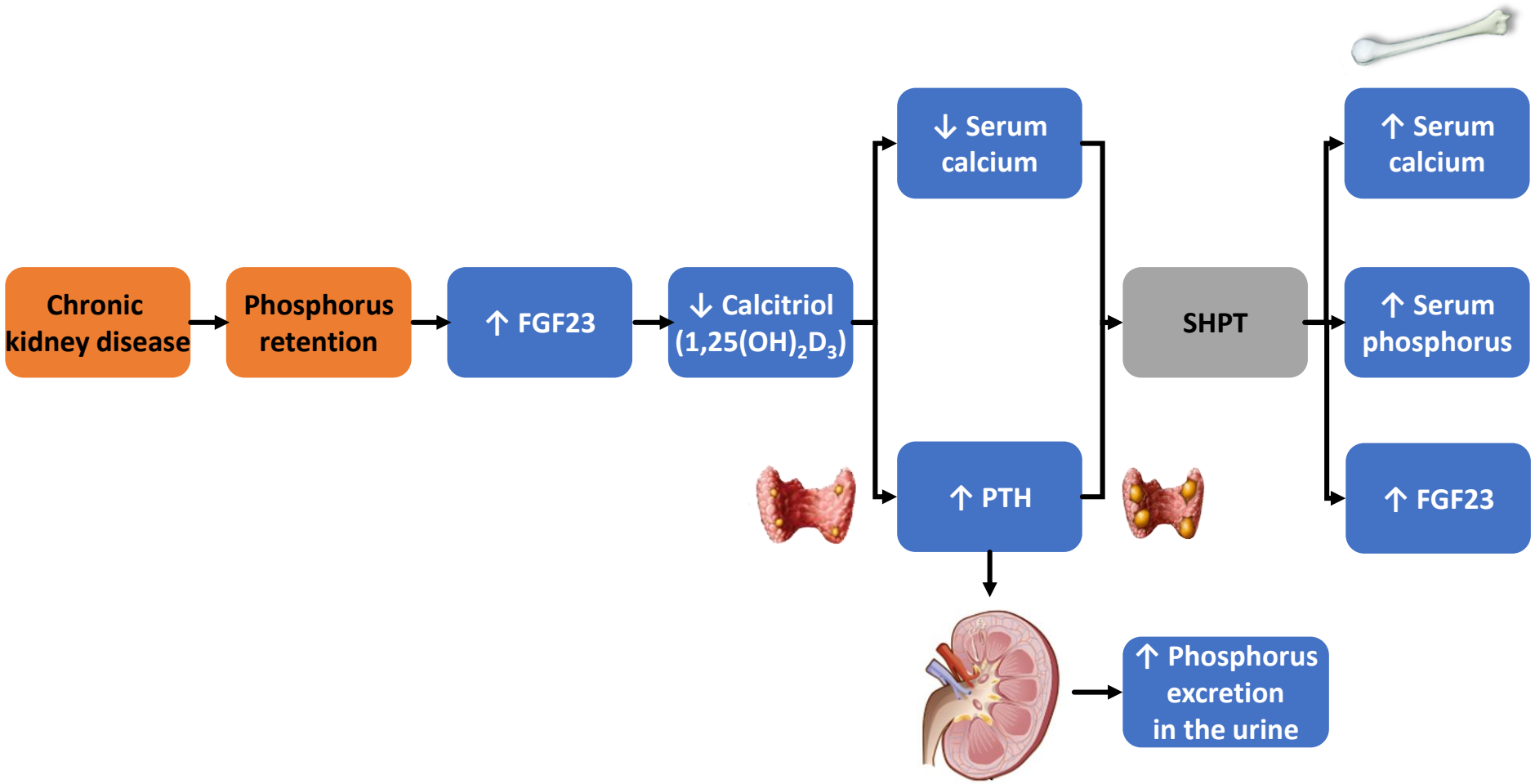


Severe calcific aortic valve stenosis revealing macroscopic areas of ulcerative calcification

***Courtesy of Dr Gabriele Lehmann, Jena, Germany.**

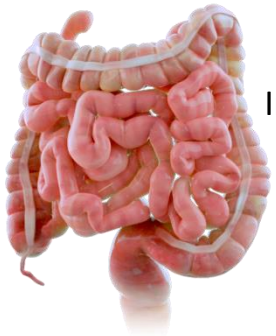
Adapted from: Cozzolino M, et al. Nephrol Dial Transplant 2014;29:1815–1820.

Pathophysiology of secondary hyperparathyroidism



Moe S, et al. Kidney Int 2006;69:1945-1953; Goodman WG. Semin Dial 2004;17:209-216; Goodman WG, et al. Kidney Int 2008;74:276-288; Goodman WG. Med Clin N Am 2005;89:631-647; Cozzolino M, et al. Am J Nephrol 2015;42:228-236; Blaine J, et al. Clin J Am Soc Nephrol 2014;10:1257-1272; Wolf M, et al. Clin J Am Soc Nephrol 2015;10:1875-1885

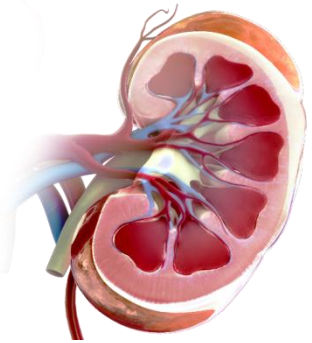
Interplay of FGF23, phosphorus, PTH and vitamin D (1,25-D) in CKD[1-3]



Increased levels of phosphorus stimulate the secretion of FGF23 from bone[1]

Phosphorus

FGF23 decreases phosphorus reabsorption in the proximal tubule and increases net phosphorus excretion[1]



1,25-D upregulates expression of FGF23[2]

FGF23

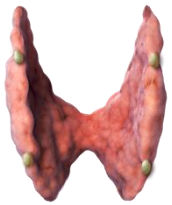
PTH upregulates expression of FGF23[3]

1,25-D

FGF23 acts as a counter-regulatory hormone, decreasing levels of 1,25-D[1]

FGF23 may suppress PTH secretion[1]

PTH



↓1-α-hydroxylase

↑24-hydroxylase

Stimulation

Suppression

Data presented are from both animal and human studies.

1. Alon US. Eur J Pediatr 2011;170:545–554; 2. Quarles LD. J Clin Invest 2008;118:3820–3828; 3. Seiler S, et al. Kidney Int 2009;(Suppl 114):S34–S42

In-Depth Review

Clin JASN 2016;11:1088–1100

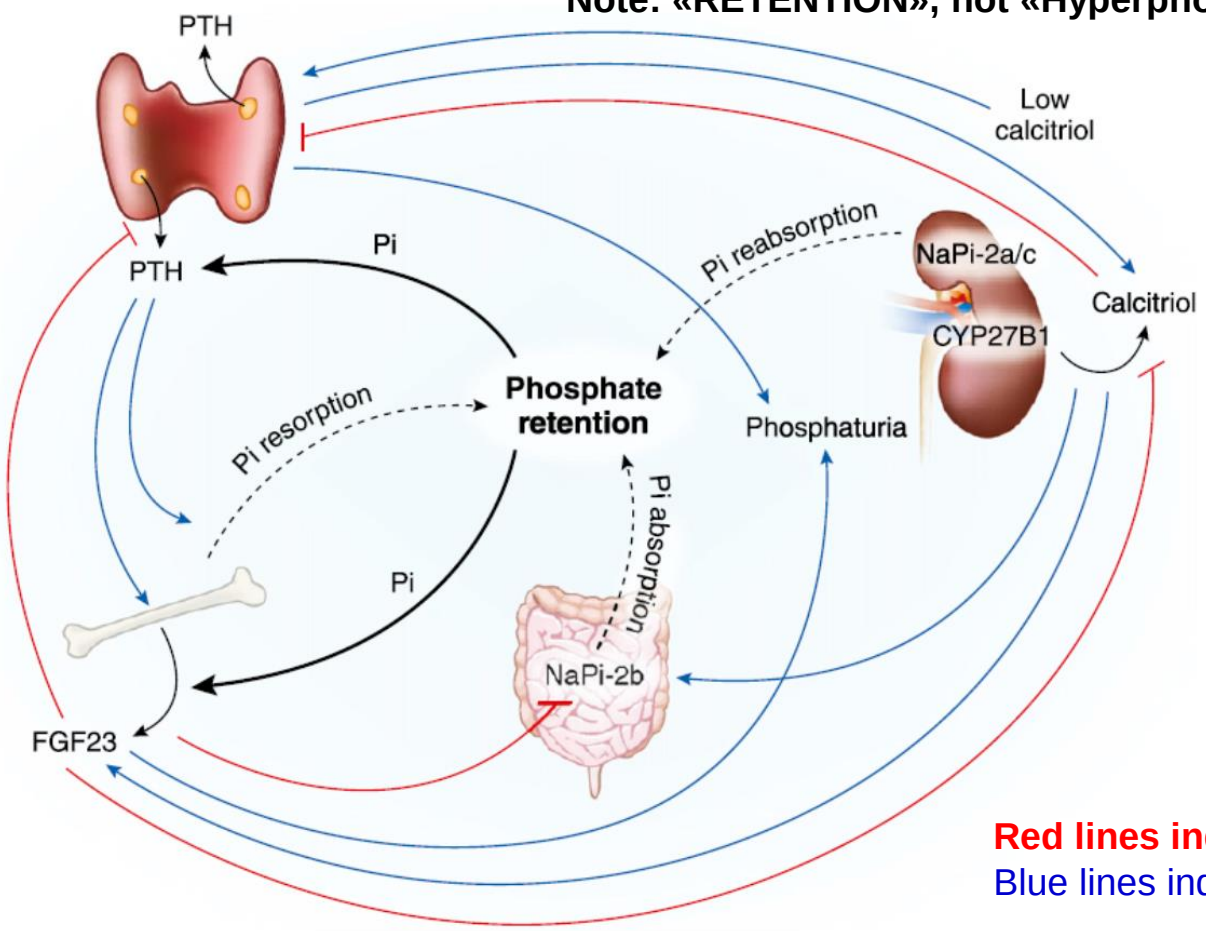
Phosphate Toxicity in CKD: The Killer among Us

Cynthia S. Ritter and Eduardo Slatopolsky

Controlling phosphate load remains the primary goal in the treatment of CKD.

Phosphate homeostasis: A complex crosstalk between the kidney, parathyroid gland, bone, and intestine

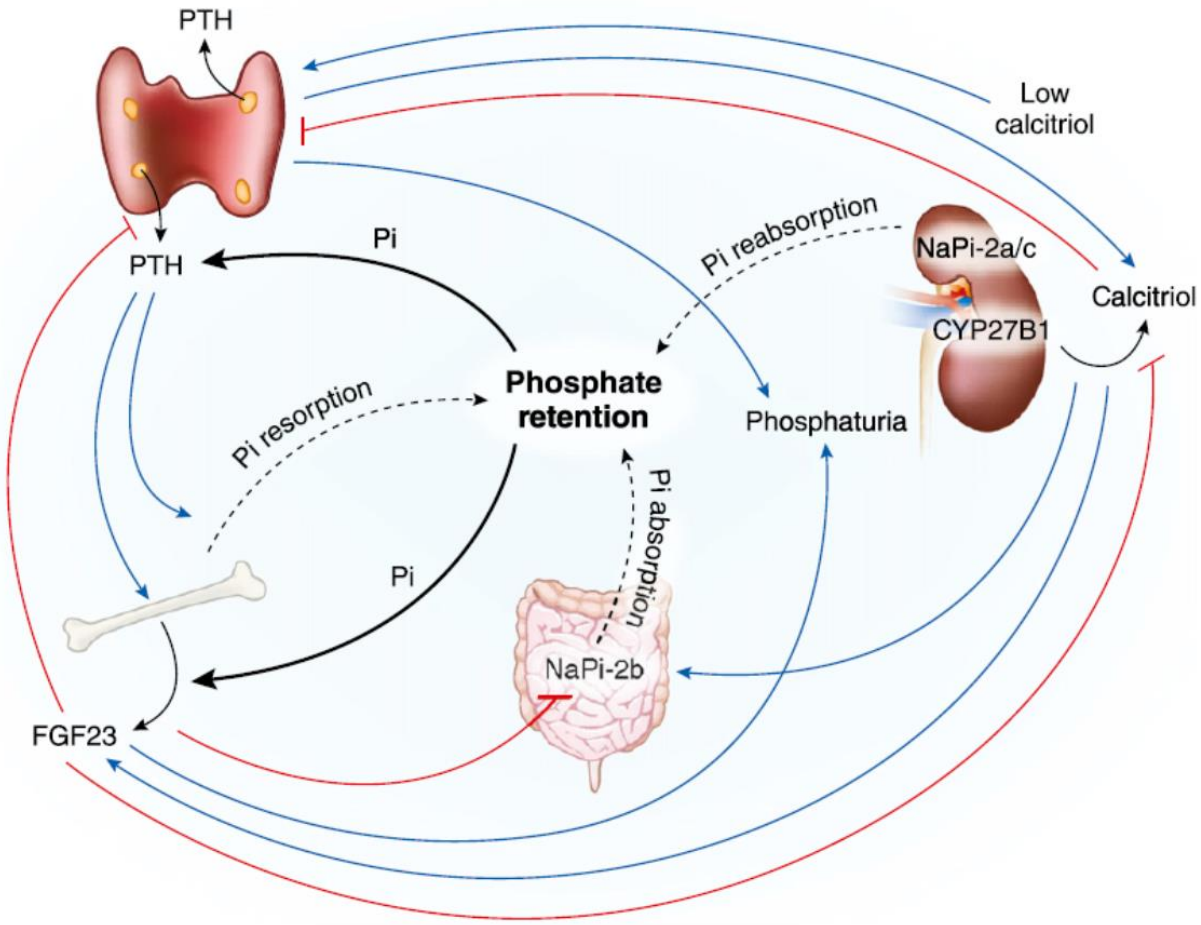
Note: «RETENTION», not «Hyperphosphatemia»



Red lines indicate inhibition
Blue lines indicate stimulation

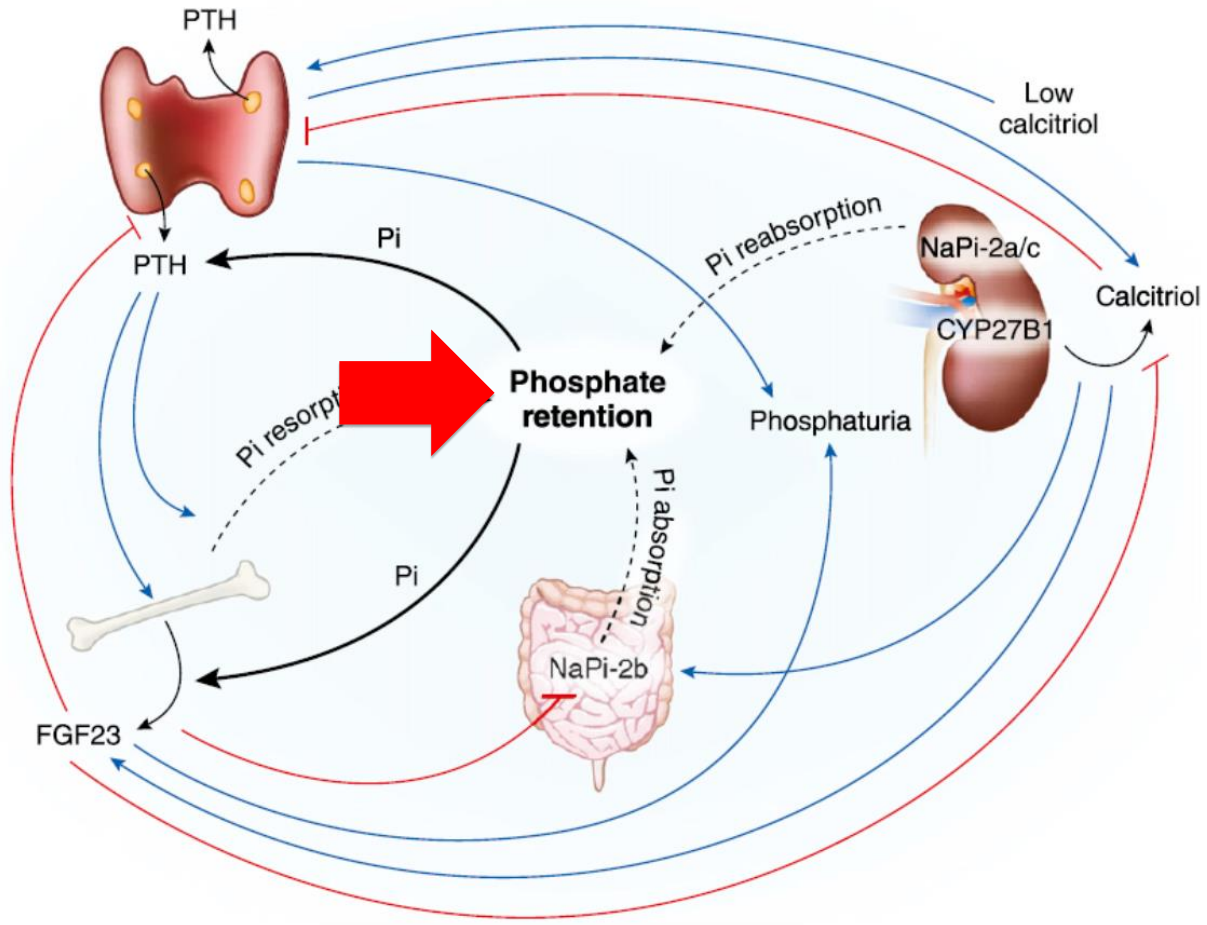
Ritter CS. Clin JASN 2016;11:1088–1100

Phosphate reabsorption in the kidney via NaPi-2a/c cotransporters, absorption in the gut via NaPi-2b cotransporter, and resorption from the bone contribute to the retention of phosphate (black dashed lines)



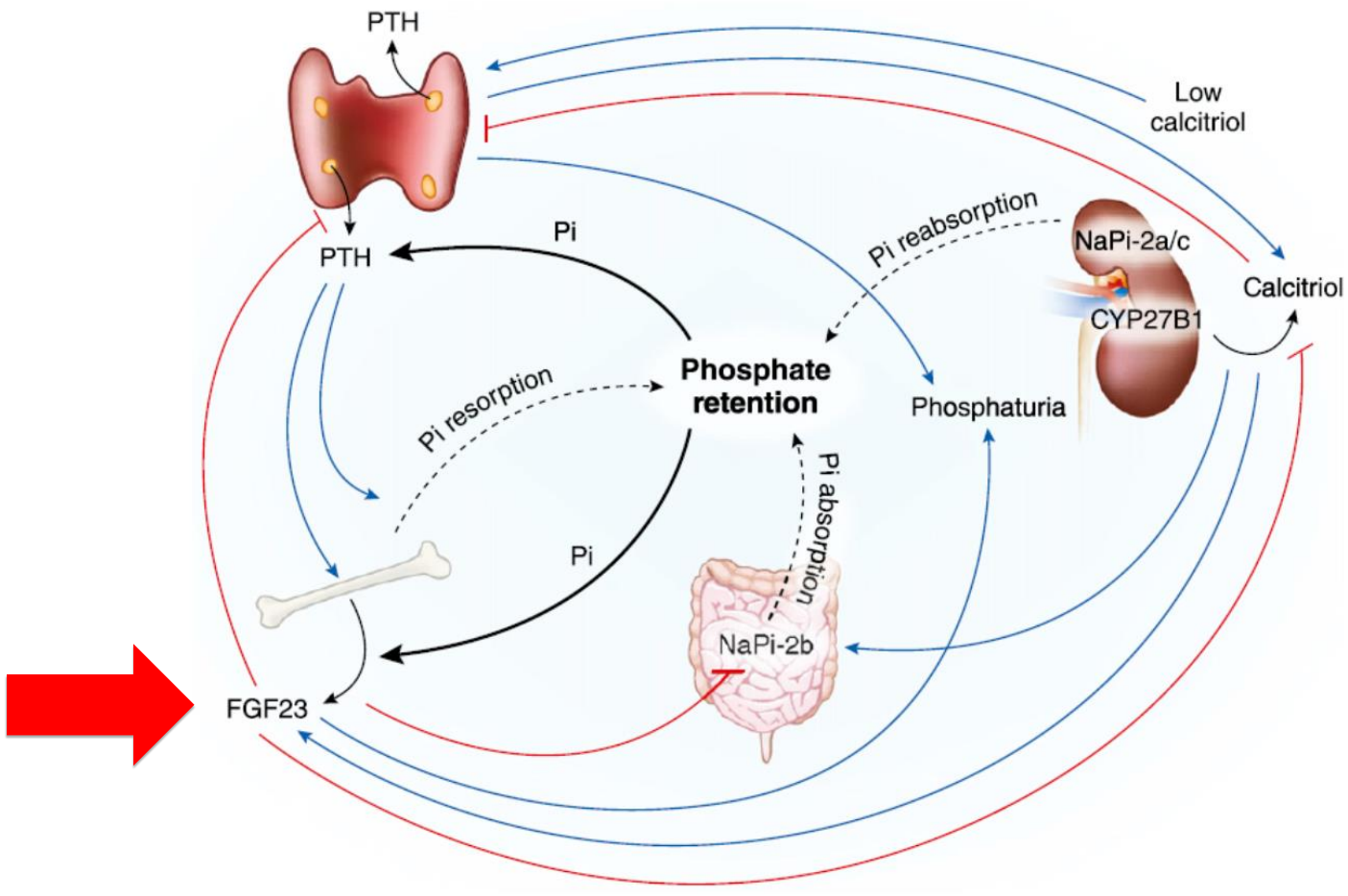
Ritter CS. Clin JASN 2016;11:1088–1100

Phosphate retention increases levels of the parathyroid hormone (PTH) and fibroblast growth factor 23 (FGF23) hormones (black solid lines), both of which inhibit phosphate reabsorption in the kidney by decreasing expression of NaPi-2a/c, resulting in phosphaturia.



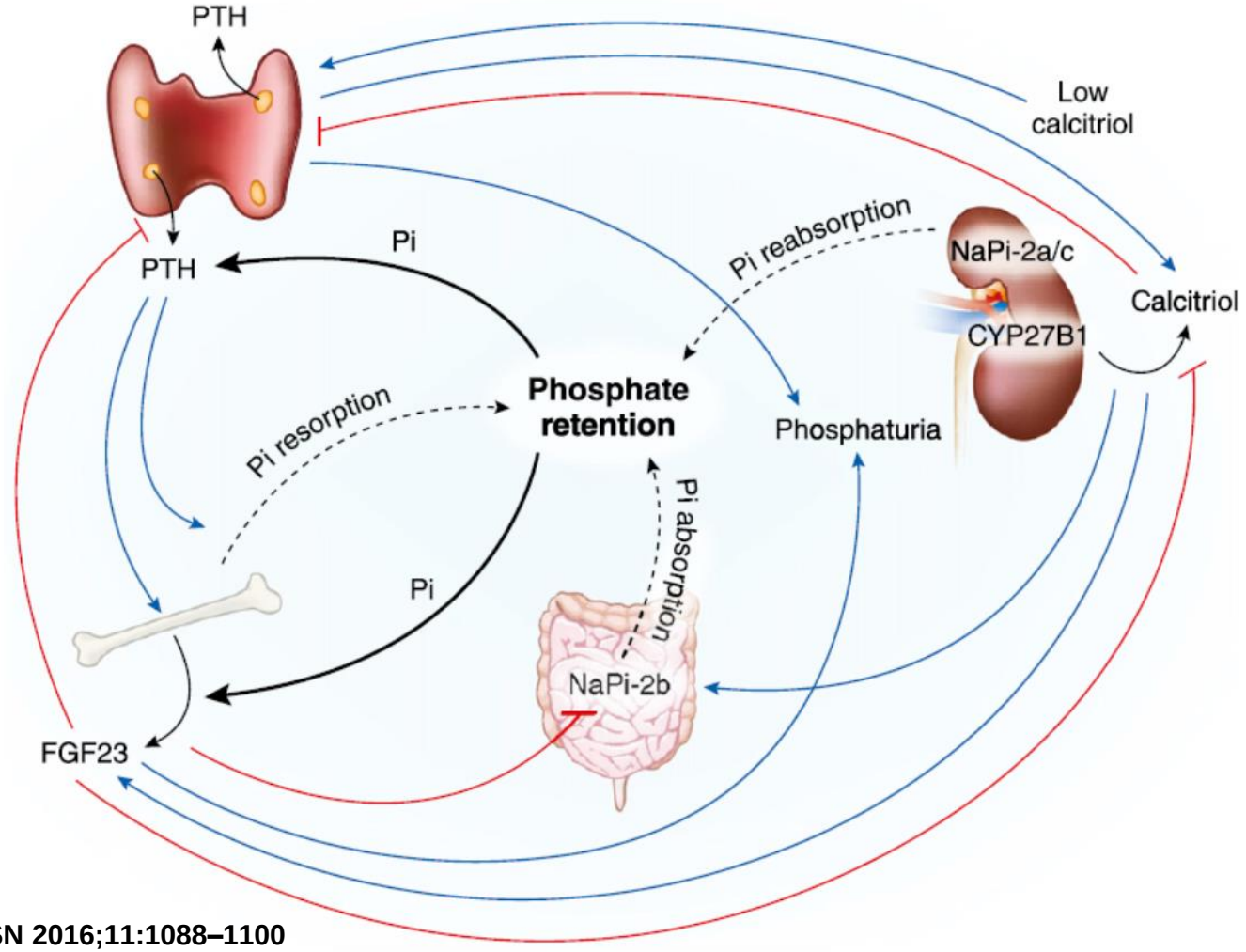
Ritter CS. Clin JASN 2016;11:1088–1100

The increase in FGF23 decreases phosphate absorption in the gut by inhibiting NaPi-2b expression and suppressing circulating calcitriol, which in turn, will inhibit intestinal absorption of phosphate.



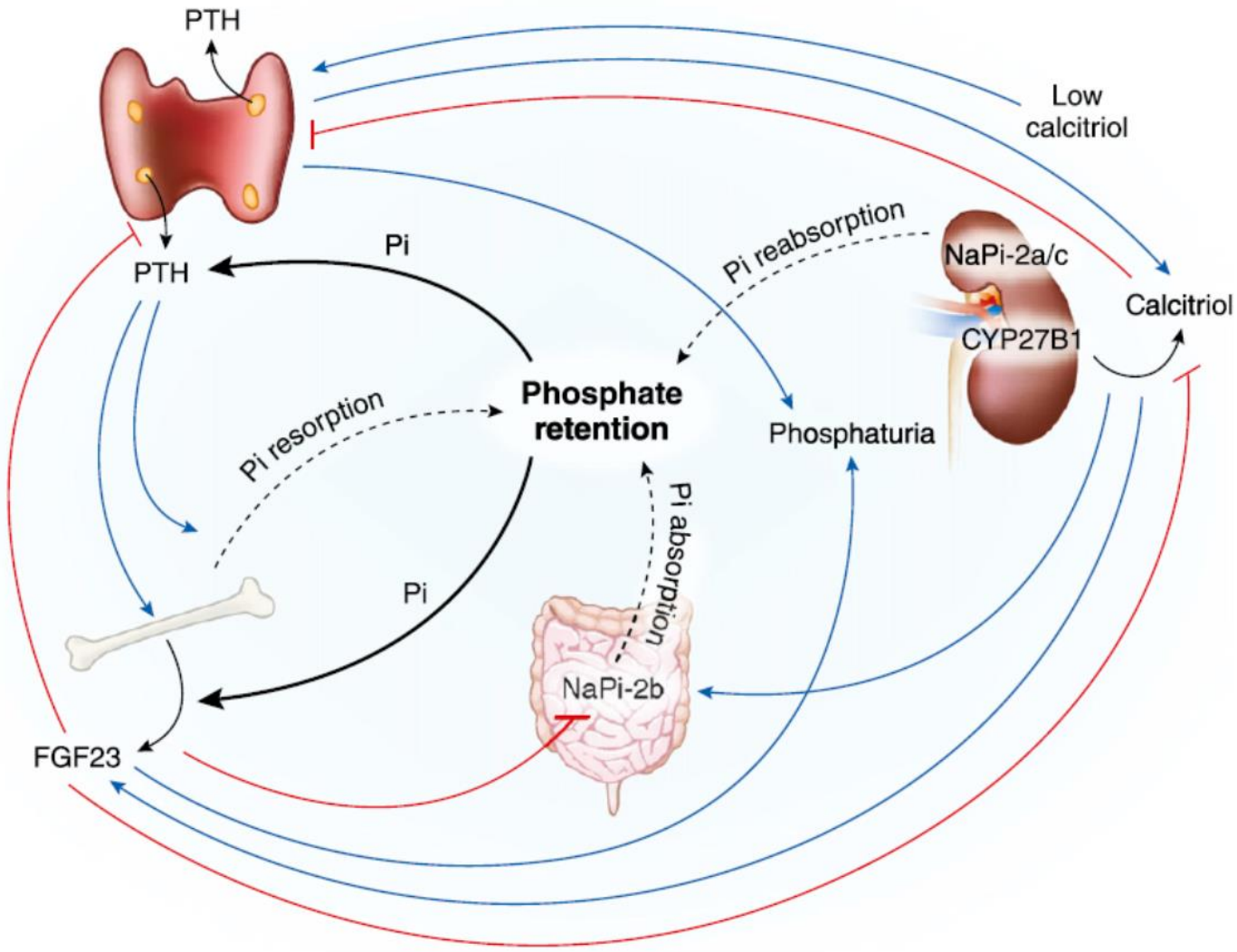
Ritter CS. Clin JASN 2016;11:1088–1100

A negative feedback loop exists between PTH and FGF23; PTH increases FGF23 (both directly and indirectly via calcitriol), whereas FGF23 inhibits PTH.
High calcitriol levels inhibit PTH and stimulate FGF23, whereas low calcitriol levels stimulate PTH.



Ritter CS. Clin JASN 2016;11:1088–1100

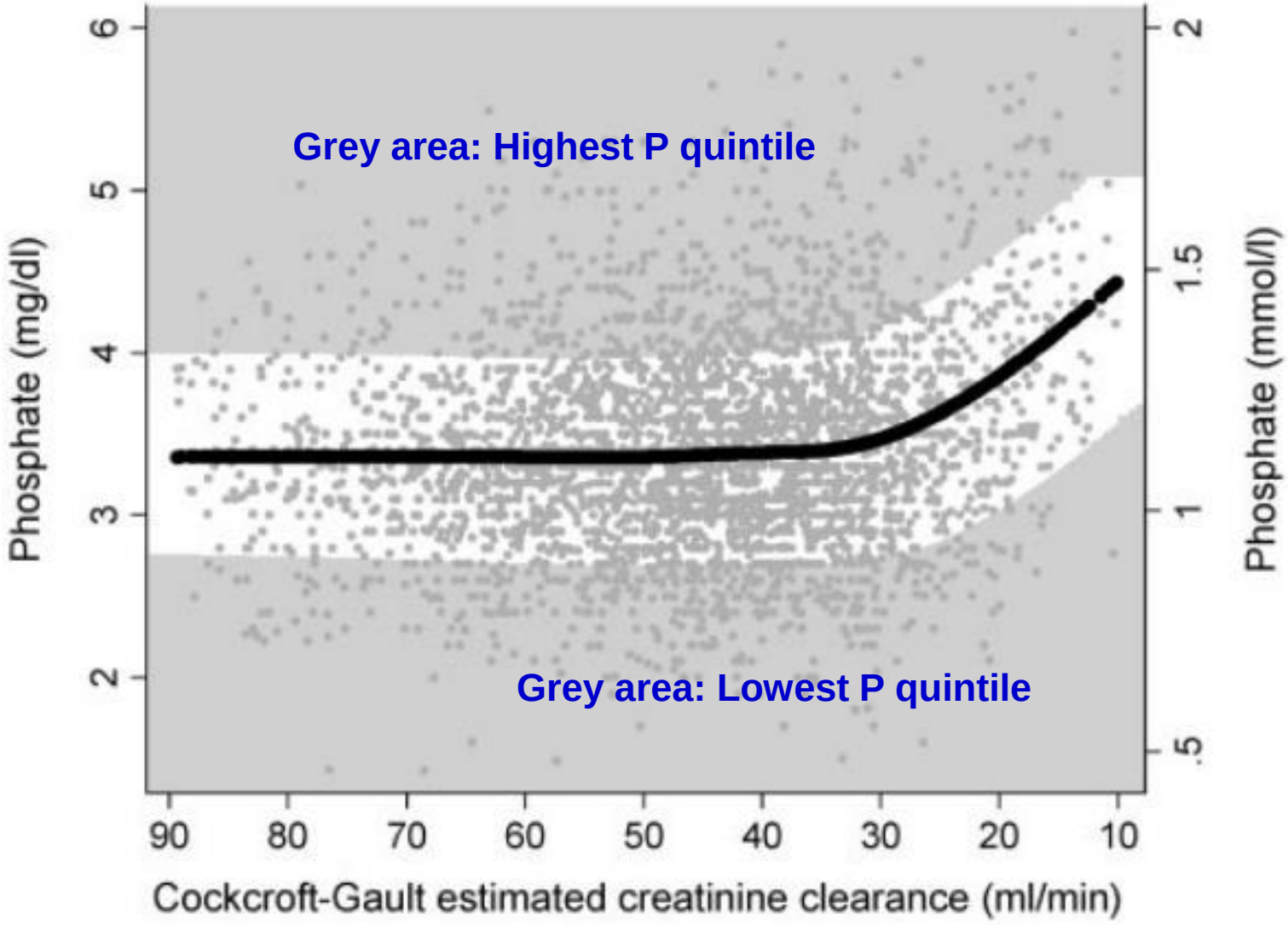
Remember: in CKD excess P retention determines high levels of FGF23 and PTH, and low levels of circulating calcitriol.



Ritter CS. Clin JASN 2016;11:1088–1100

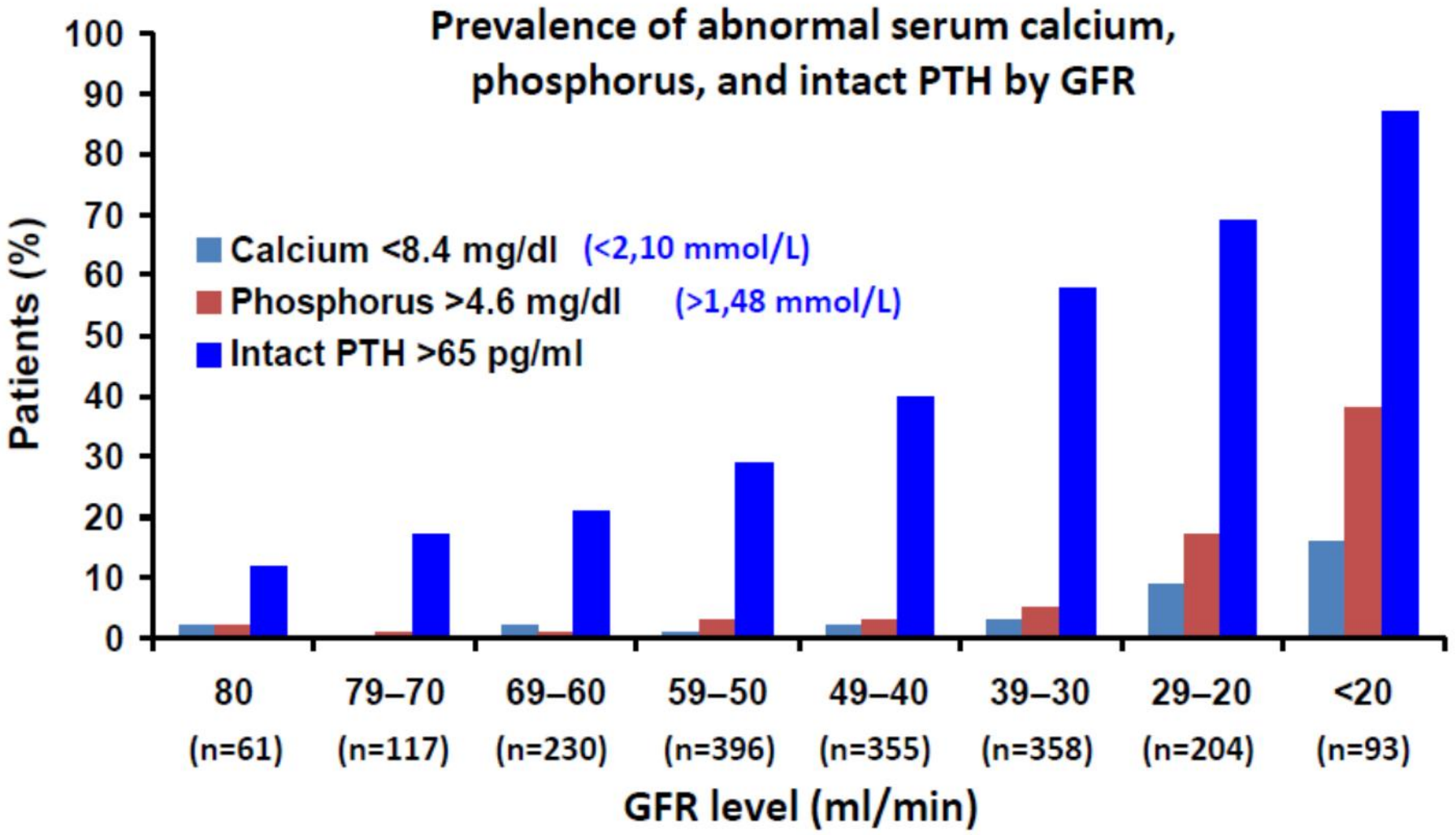
Livelli di fosfatemia vs. eGFR

Mean serum phosphate levels as a function of creatinine clearance



Kestenbaum, *J Am Soc Nephrol* 16: 520-528, 2005

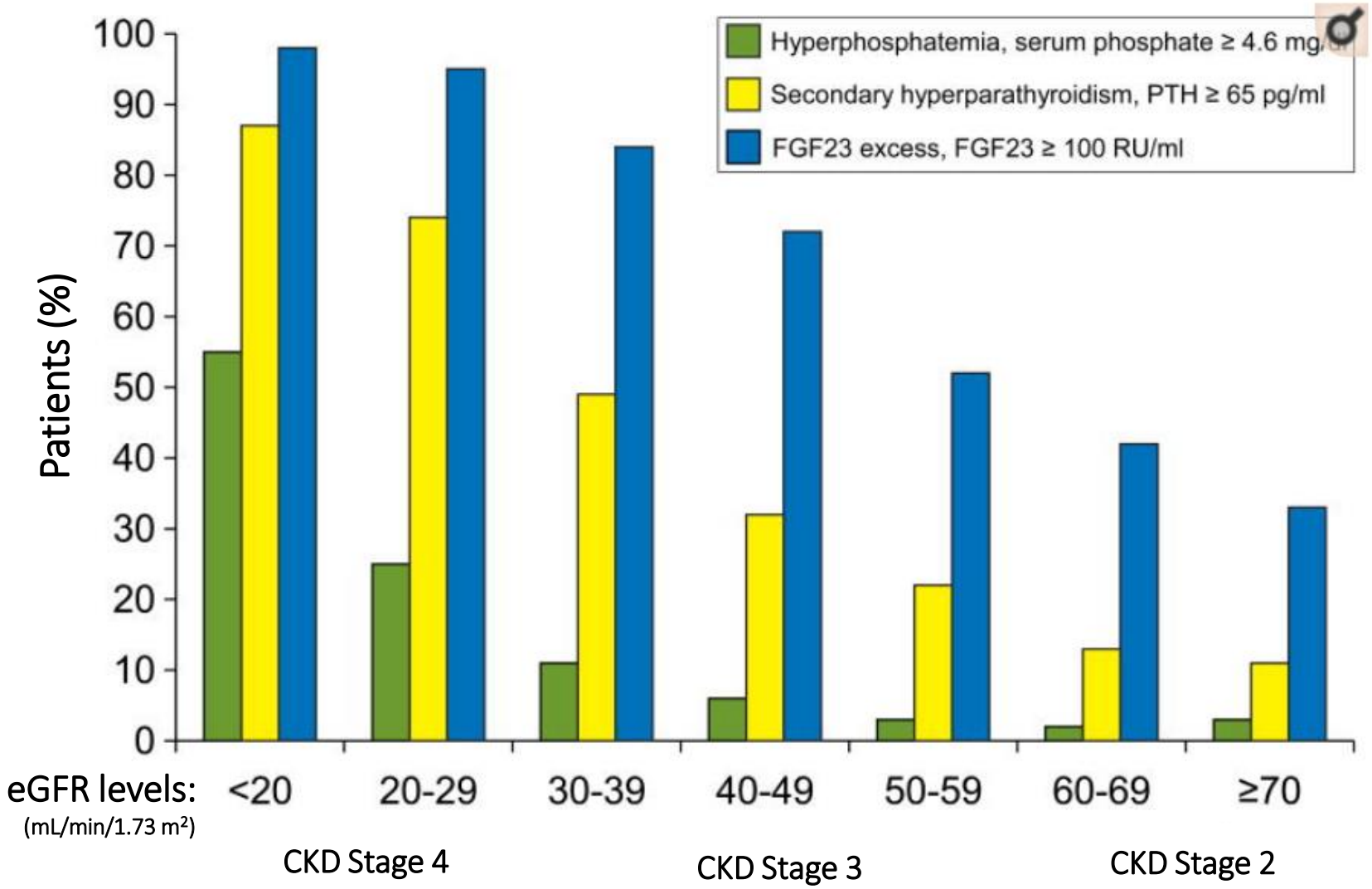
Secondary hyperparathyroidism occurs early in CKD, before measurable abnormalities in Ca and P



Levin A et al. Kidney Int 2007;71:31-8

Elevated FGF23 levels may be the earliest predictor of disordered mineral metabolism in CKD

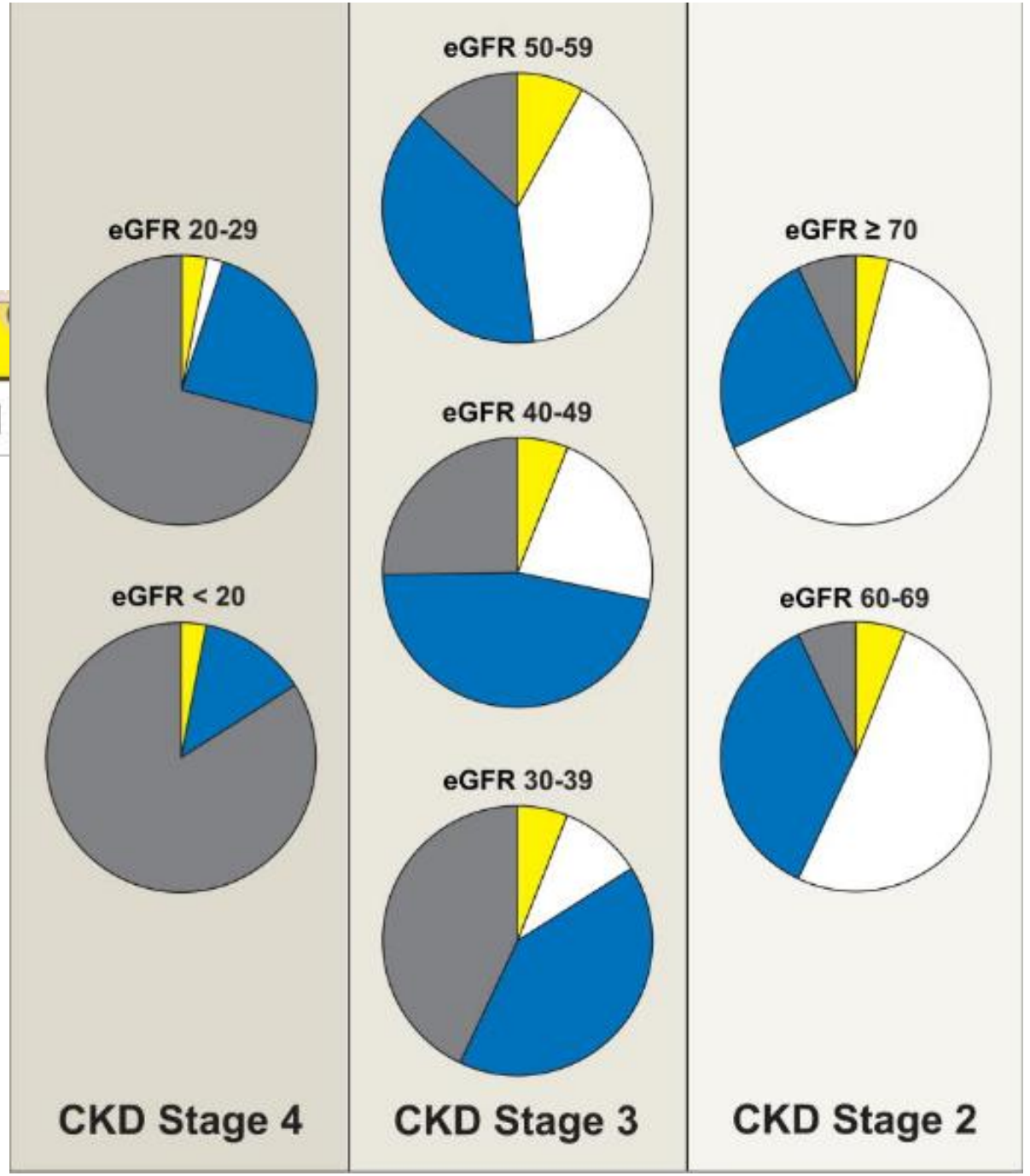
FGF 23 is elevated before PTH and phosphate in CKD



Isakova T, et al. Kidney Int 2011;79:1370–1378.

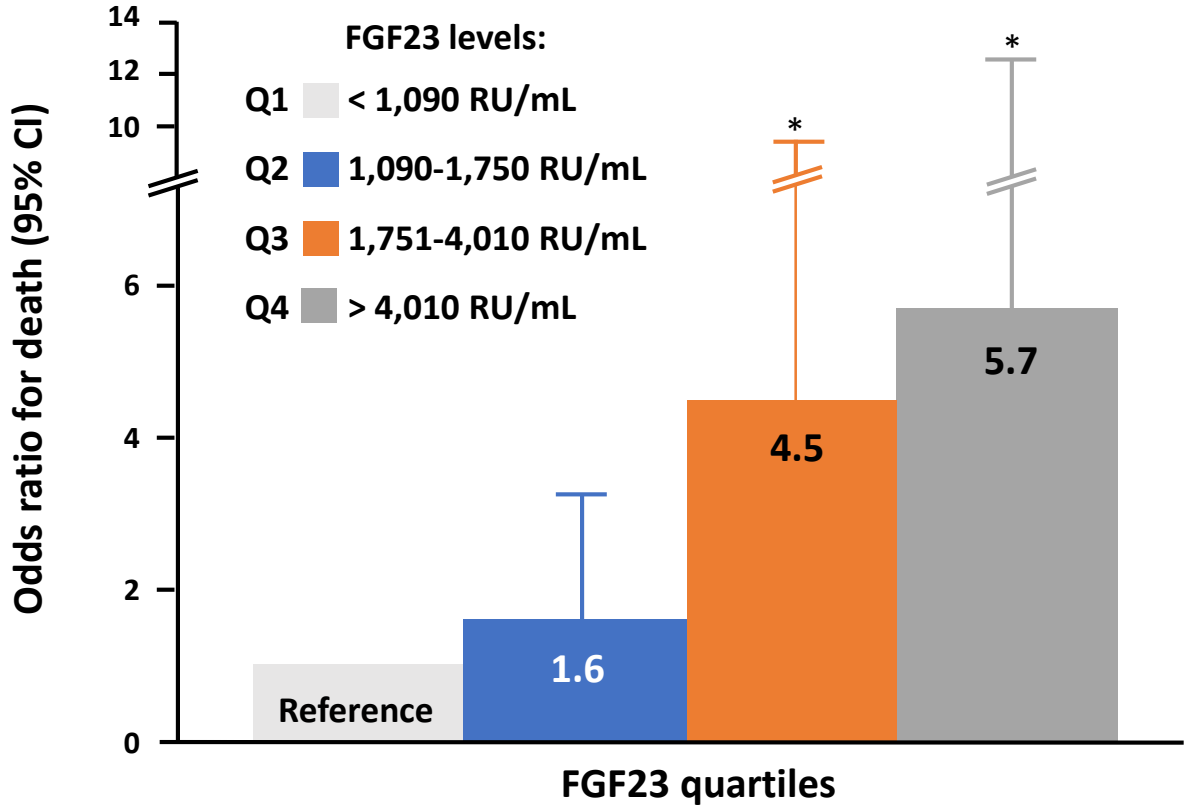
Proportions of participants with normal or high FGF23 and PTH levels within each eGFR category

High FGF23/High PTH	High PTH/Normal FGF23
High FGF23/Normal PTH	Normal FGF23/Normal PTH



Isakova T, et al. Kidney Int 2011;79:1370–1378.

Patients in the higher quartiles of FGF23 levels have a higher risk of mortality compared with subjects in the lower quartiles

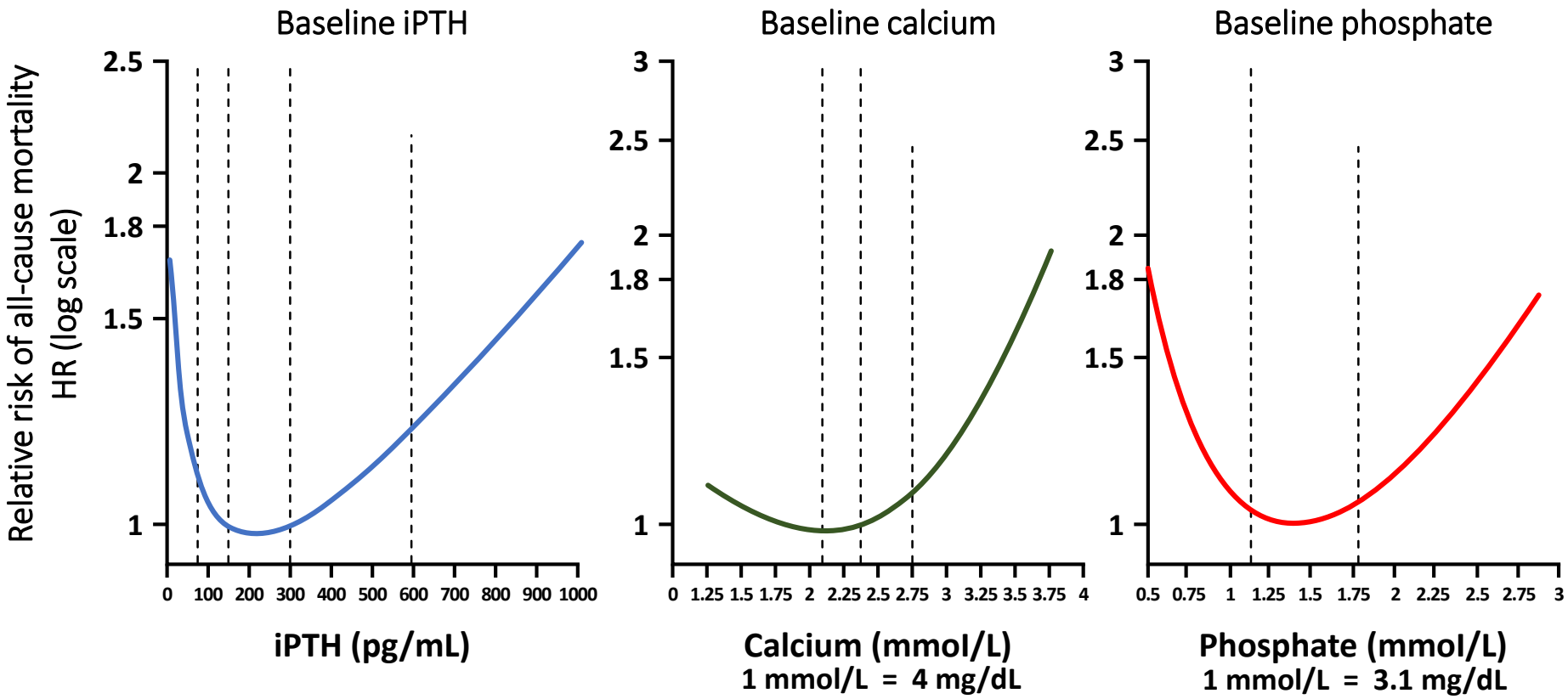


Prospective analysis of the relationship between increased FGF23 levels and mortality, independent of established risk factors and serum phosphate levels, in patients beginning haemodialysis; data for multivariable adjusted model are presented.

N = 400; *p < 0.05
Q = quartile; RU = relative units.
Gutiérrez OM, et al. N Engl J Med 2008;359:584–592.

Mortality risk of CKD patients increases if serum iPTH, Ca and P levels are outside target ranges

Analyses based on observational data. Association between markers of mineral and bone disease and clinical outcomes was examined in 7970 patients over a median of 21 months.



Adapted from: Floege J, et al. Nephrol Dial Transplant 2011;26:1948-1955.

Patients with PTH > 900 pg/mL have a 72% increased risk of a fracture vs patients with PTH 150-300 pg/mL

PTH (pg/mL) (n/N pts)	RR of hip fracture (95% CI)	RR of any fracture (95% CI)
< 150 (3523/8162)	1.27 (0.78, 2.06)	1.05 (0.80, 1.38)
150–300 (2267/8162)	**1.00 (Ref.)**	**1.00 (Ref.)**
301–600 (1524/8162)	1.19 (0.63, 2.26)	1.24 (0.88, 1.76)
601–750 (295/8162)	0.33 (0.05, 2.37)	0.86 (0.41, 1.77)
751–900 (185/8162)	0.62 (0.08, 4.87)	1.03 (0.35, 3.08)
> 900 (368/8162)	**1.14 (0.34, 3.80)**	**1.72* (1.02, 2.90)**

*$p < 0.05$

Jadoul M, et al. Kidney Int 2006;70:1358–1366.

Arterial or valvular calcification is strongly associated with cardiovascular morbidity and mortality

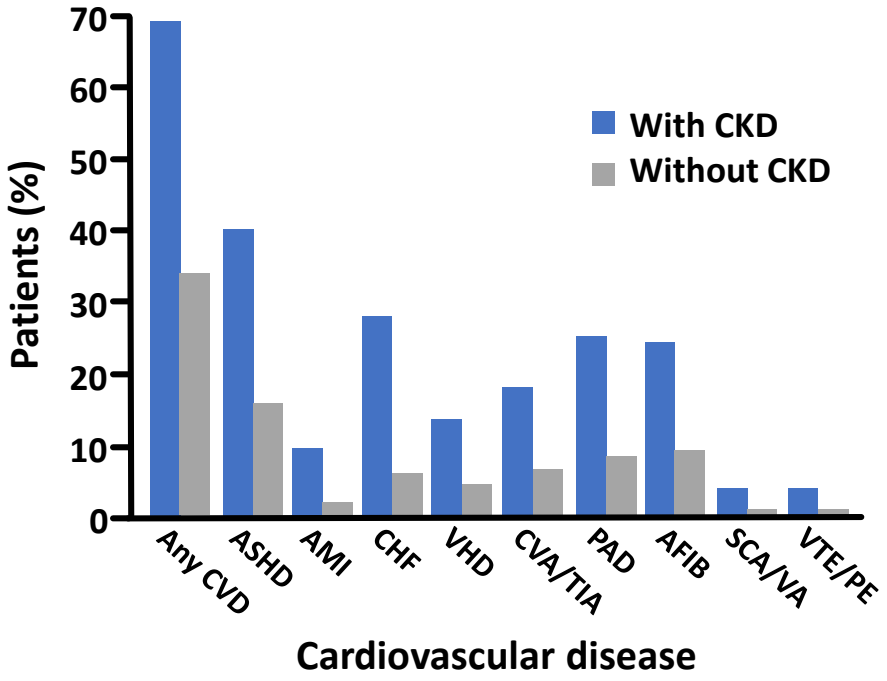
Calcification in dialysis patients

- 70% of patients have significant coronary artery and aortic calcification[1]
- 50% of patients have calcified valves[1]
- 50% of cardiovascular death may be associated with abnormal tissue calcification in patients treated with dialysis[2]

Cardiovascular mortality

- 39% of all deaths in patients on dialysis are related to cardiovascular mortality[3]

Prevalence of CVD in patients with or without CKD[4]



69% of patients with CKD have CVD
vs 34 % of patients without CKD

1. Moe S. Kidney Int 2006;70:1535–1536; 2. Razzaque M, et al. Nephrol Dial Transplant 2005;20:2032–2035; 3. de Jager DJ, et al. JAMA 2009;302:1782–1789; 4. US Renal Data System. Volume 1: 2016; https://www.usrds.org/2016/view/Default.aspx

J Nephrol
DOI 10.1007/s40620-015-0202-4

ORIGINAL ARTICLE

Management of CKD-MBD in non-dialysis patients under regular nephrology care: a prospective multicenter study

Maurizio Gallieni[1] · Luca De Nicola[2] Domenico Santoro[3] · Gina Meneghel[4] · Marco Formica[5] · Giuseppe Grandaliano[6] · Francesco Pizzarelli[7] · Maria Cossu[8] · Giuseppe Segoloni[9] · Giuseppe Quintaliani[10] · Salvatore Di Giulio[11] · Antonio Pisani[12] · Moreno Malaguti[16] · Cosimo Marseglia[13] · Lamberto Oldrizzi[14] · Mario Pacilio[2] · Giuseppe Conte[2] · Antonio Dal Canton[15] · Roberto Minutolo[2]

CKD stages 3b, 4, and 5

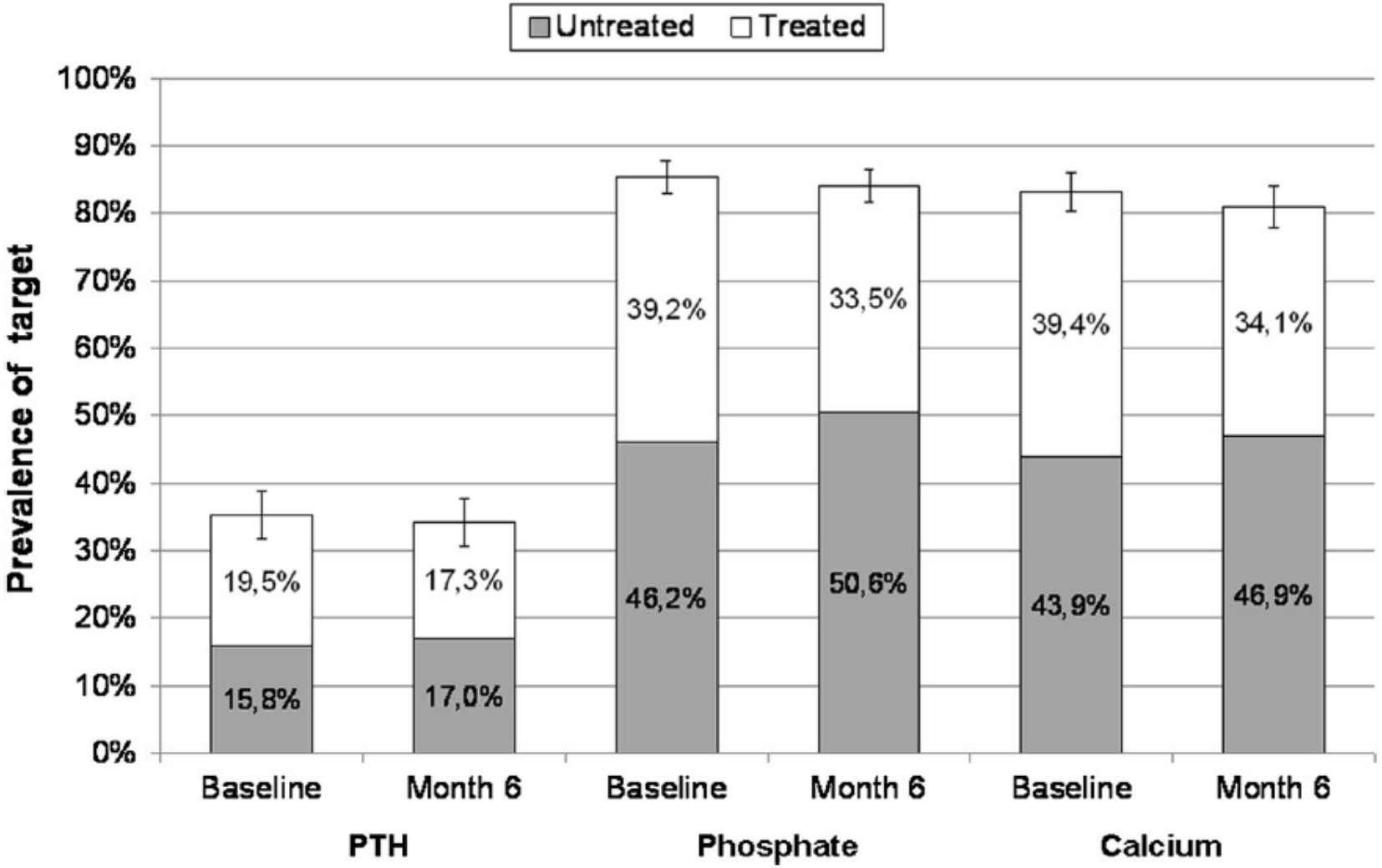
Patients not on target: PTH 65%, Ca 15%, P 19%

Treatments:

- **Low protein diet: 26 % of patients**
- **phosphate binders: 17.3 %**
- **vitamin D: 50.5 %.**

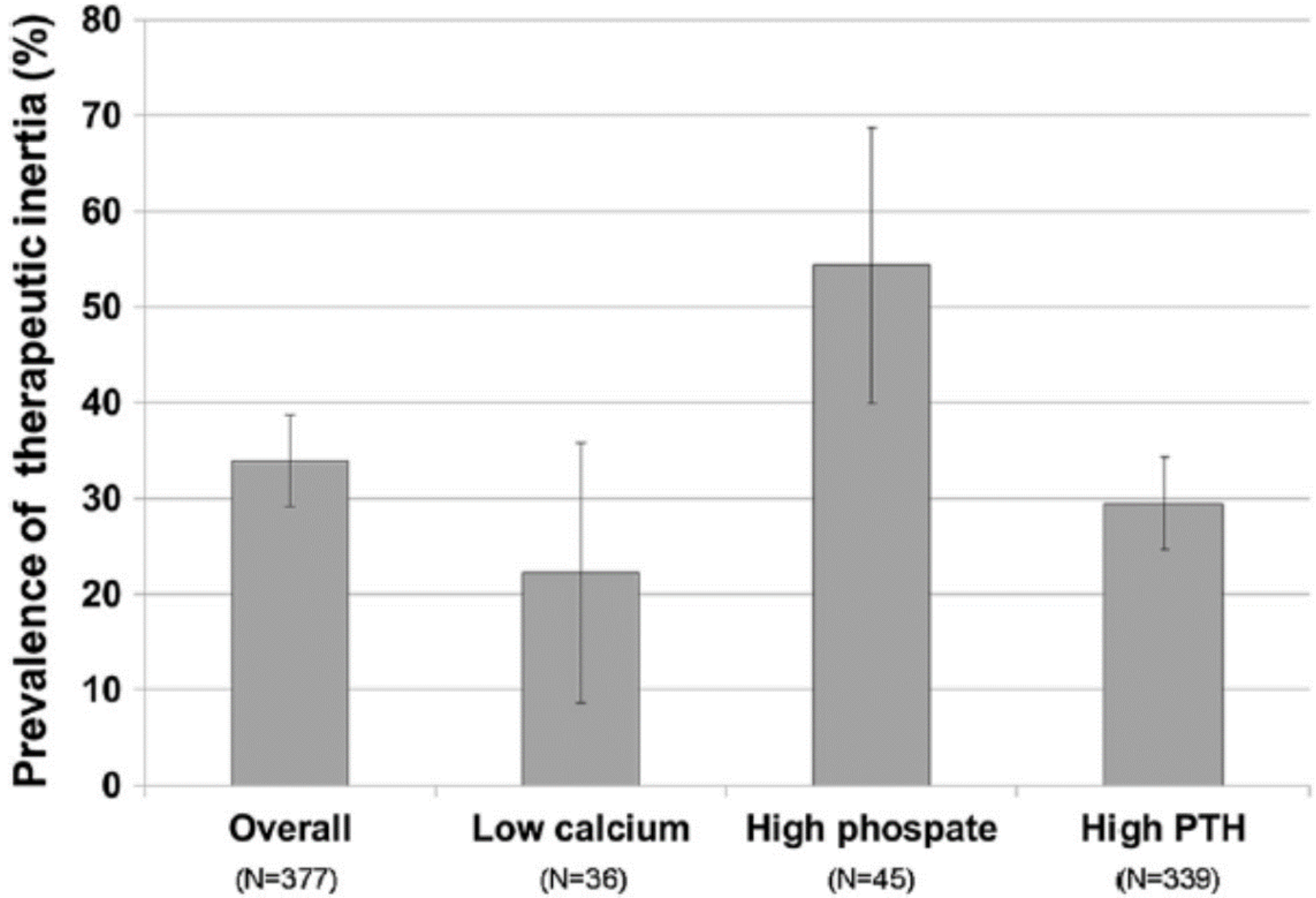
Gallieni M et al. J Nephrol 2016; 29:71-78

Achievement of center-specific targets



Gallieni M et al. J Nephrol 2016; 29:71-78

Prevalence of therapeutic inertia



Gallieni M et al. J Nephrol 2016; 29:71-78