Le Phosphate en Dialyse

DU Strasbourg, 22 Novembre 2019

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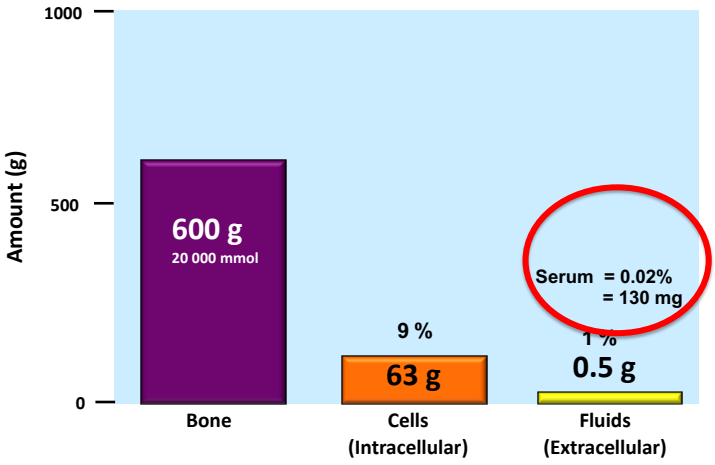
1

Phosphate Physiology and Body Distribution

Functions

Mineral : Teeth/Bone
Energy (ATP)
pH regulation
Signal transduction
Cell Membrane
Nucleic acids
2-3 DPG



- The most abundant anion in the body (700 g = 23 000 mmol)
- Intracellular (80-120 mmol/l IC and only 1-1.5 mmol/l plasma)
- Minimum needs in a healthy adult : 300 mg/day

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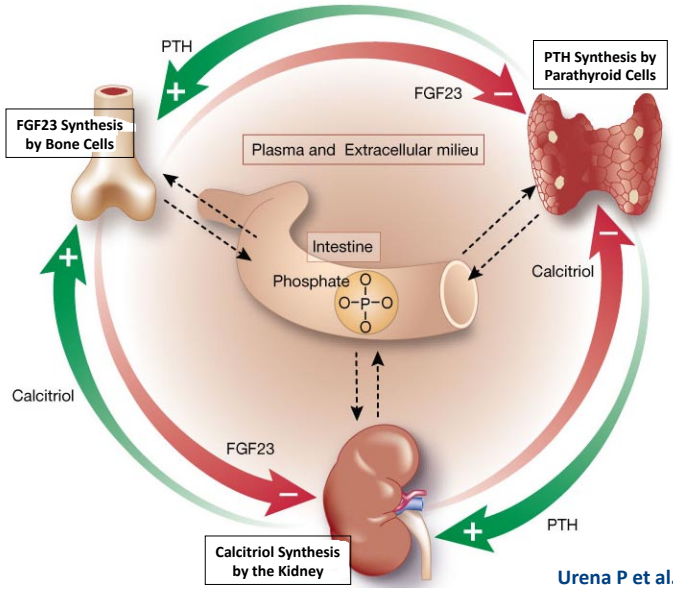
Phosphatemia Regulation

3

Regulation of Serum Phosphate



Urena P et al. Kidney Int, 2011

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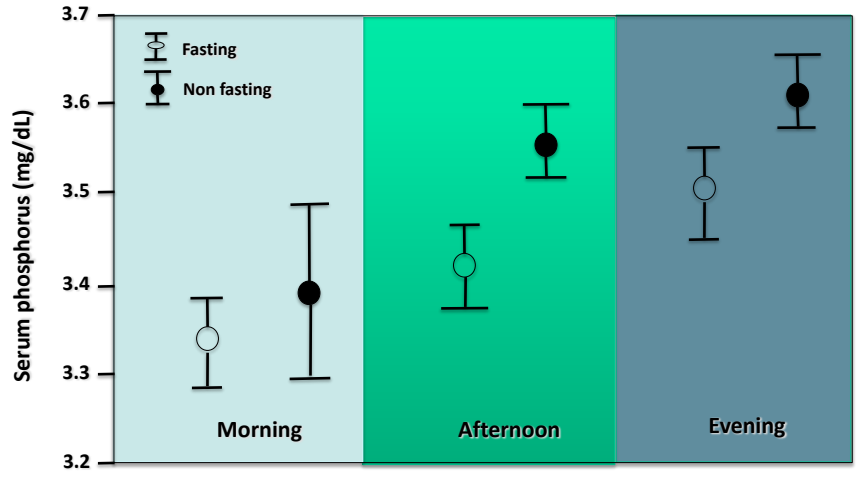
Serum Phosphate Concentration

Total Plasma Phosphate = 3,9 mmol/l

Inorganic Phosphate = 0,80 – 1,45 mmol/L (2.6 to 4.6 m/dL)

Orthophosphate et pyrophosphate

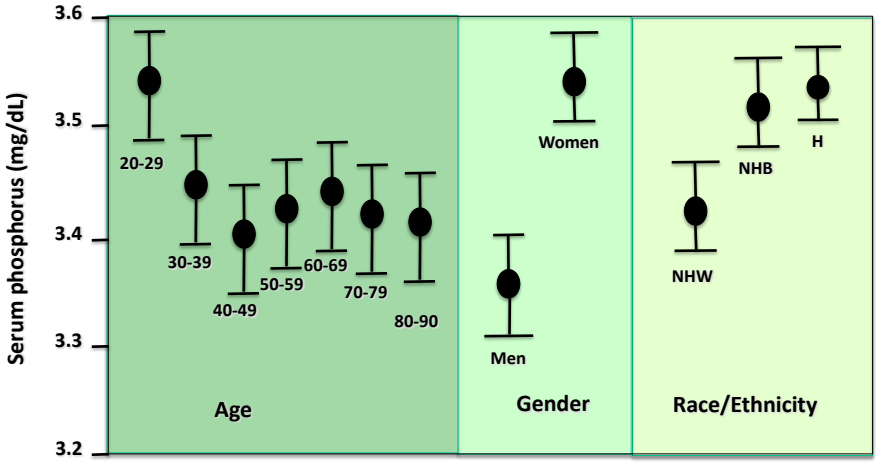


15,513 subjects

De Boer IH, et al., NHANES III. AJKD 53:399-407, 2009

5

Serum Phosphate Concentration



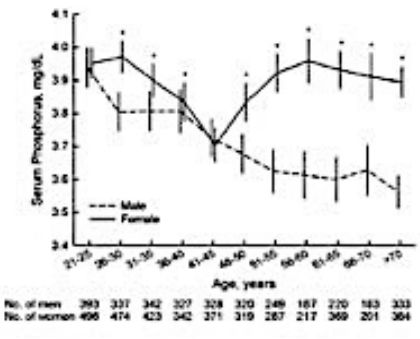
15,513 subjects

De Boer IH, et al., NHANES III. AJKD 53:399-407, 2009

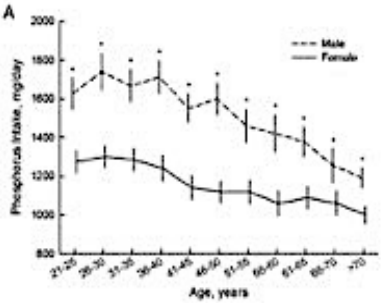
6

Serum Phosphate Concentration

Phosphatemia / Gender / Age



Phosphate Intake / Gender / Age



The phosphatemia varies according to gender and age

Daily phosphate intake decreases with age

NHANES III, 2009

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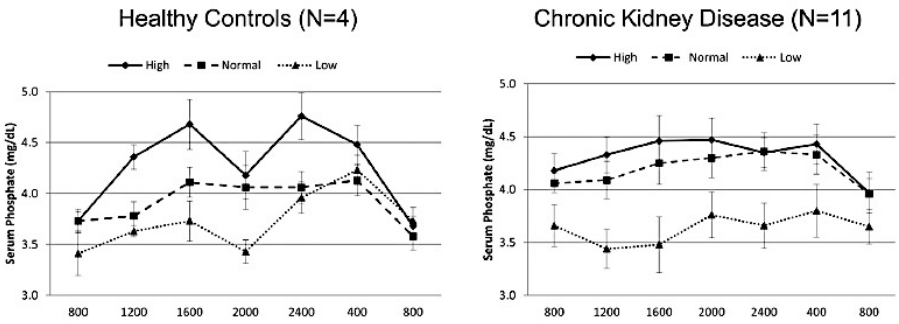
Serum Phosphate Concentration



The nictemeral rhythm is flat in CKD subjects

Fasting phosphatemia was higher in patients with high phosphate intake

Ix J, Am J Clin Nutr 2014

8

Phosphatemia According to Renal Function: NHANES 2003-2006

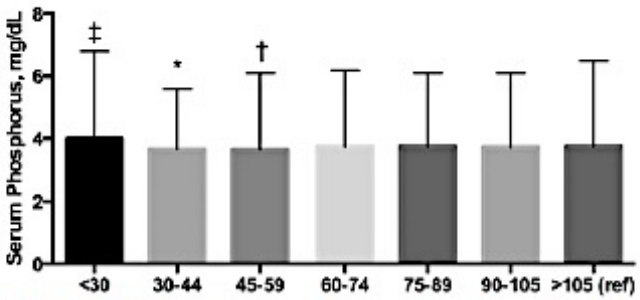


FIGURE 1 Median and range of serum phosphorus in mg/dL across kidney function level categories in NHANES 2003–2006 reported as the eGFR from the Chronic Kidney Disease Epidemiology Collaboration 2009 equation in mL · min^{-1} · 1.73 m^{-2}. *$P < 0.05$, †$P < 0.01$, ‡$P < 0.001$; compared with reference group, eGFR >105 mL · min^{-1} · 1.73 m^{-2}. eGFR, estimated glomerular filtration rate.

Moore L et al. Am J Clin Nut 102:444-453, 2015

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Phosphatemia and Mortality

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Serum Phosphate Concentration and Longevity

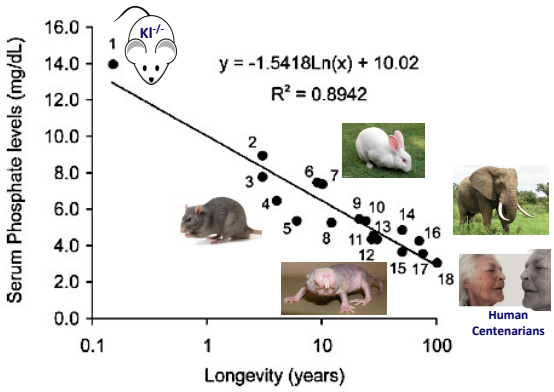

Fig. 2. Relation between longevity and serum phosphate in mammals. 1: *Klotho*$^{-/-}$ mouse, 2: Mouse, 3: Rat, 4: Hamster, 5: Gerbil, 6: Nutria, 7: Rabbit, 8: Guinea pig, 9: Sheep, 10: Squirrel, 11: Porcupine, 12: Naked mole rat, 13: Flying fox, 14: Bear, 15: Rhinoceros, 16: Elephant, 17: Human, 18: Human (centenarian). Serum phosphate levels are average or median values, whichever available in literatures (Asadi et al., 2007; Feldhamer et al., 2003; Field et al., 1998; Gorbunova et al., 2008; Heard et al., 2006; Holliday, 1995; Kuro-o et al., 1997; Moreau et al., 2003; Munson et al., 1998; Passeri et al., 2008; Pugh, 2002; Ramsay, 2003; Segawa et al., 2007; Thrall et al., 2004; Tuntasuvan et al., 2002; Yahav et al., 1993).

Kuro-O M. Mechanisms of Ageing and Development 131:270-275, 2010

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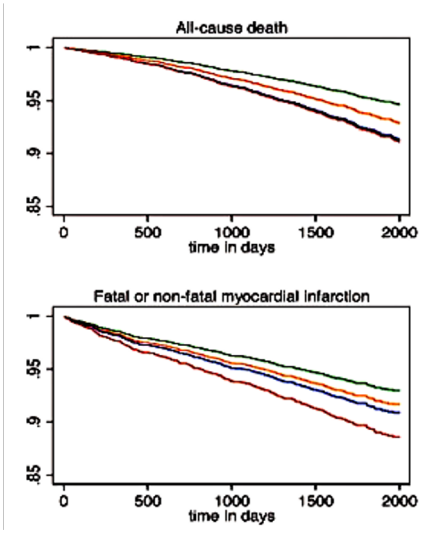
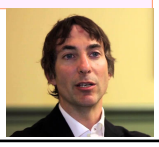
Serum Phosphate Concentration and Risk of Mortality in Subjects with Normal Renal Function



CARE Study

- Post-hoc analysis from CARE study
- 60-month follow-up
- Pravastatin vs Placebo
-375 death over 60 months
- Baseline serum PO_4 vs adjusted mortality risk

-A grade risk of death rate vs serum PO_4 seen
- Serum PO_4 < 3.5 mg/L (1.13 mM) hazard ratio = 1.27 (1.02-1.59) compared to serum PO_4 > 3.5
-Higher levels of serum PO_4 associated with new heart failure, myocardial infraction, and coronary death or nonfatal MI



Tonelli M et al., Circulation 112:2627-2633, 2005

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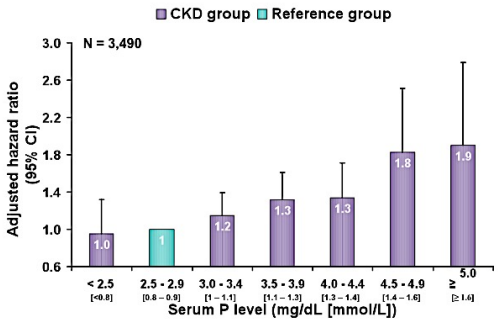
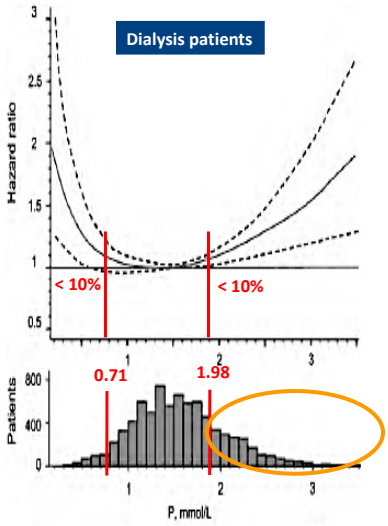
Phosphate Concentration and Risk of Mortality in CKD Patients





3490 CKD patients (veterans)

23% du HR x 1 mg/dl

Kestenbaum, B., et al. JASN 16:520-528, 2005

Fouque D., et al. NDT 28:360-367, 2013

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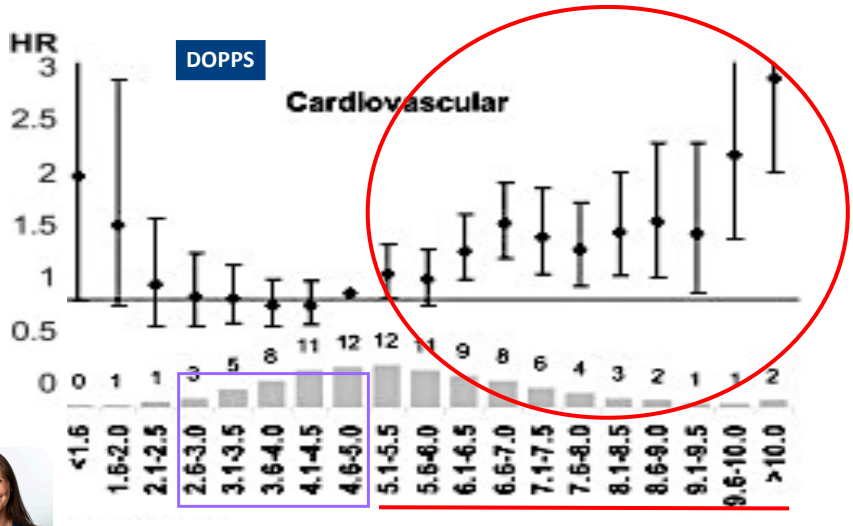
Phosphate Concentration and Risk of Mortality in CKD Patients



Tentori F. et al. DOPPS 2008

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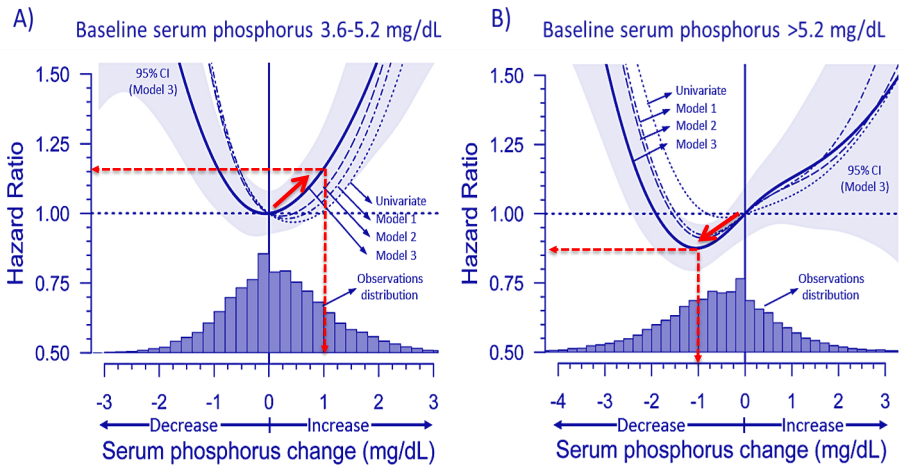
Changes in Serum Phosphate Concentration and Risk of Mortality in CKD Patients: Cosmos



Fernandez-Martin JL et al. NDT 30:1542-1551, 2015

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KDIGO Recommendation

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4- Phosphatémie

2009 : 4.1.1. Chez les patients avec MRC aux stades 3a-5D il est suggéré de maintenir la phosphatémie dans les limites normales. Chez les patients avec MRC stades 5D il est suggéré de faire baisser la phosphatémie vers des valeurs normales.

2017 : 4.1.2. Chez les patients avec MRC stades 5D il est suggéré de faire baisser la phosphatémie vers des valeurs normales (2C).

Argumentaire : *Nous ne disposons pas de données démontrant que le maintien d'une phosphatémie normale ait un bénéfice palpable chez les patients avec MRC aux stades 3a-4, alors qu'il peut exister certains problèmes de sécurité d'emploi avec certains chélateurs du phosphate. Le traitement doit viser les hyperphosphatémies franches.*

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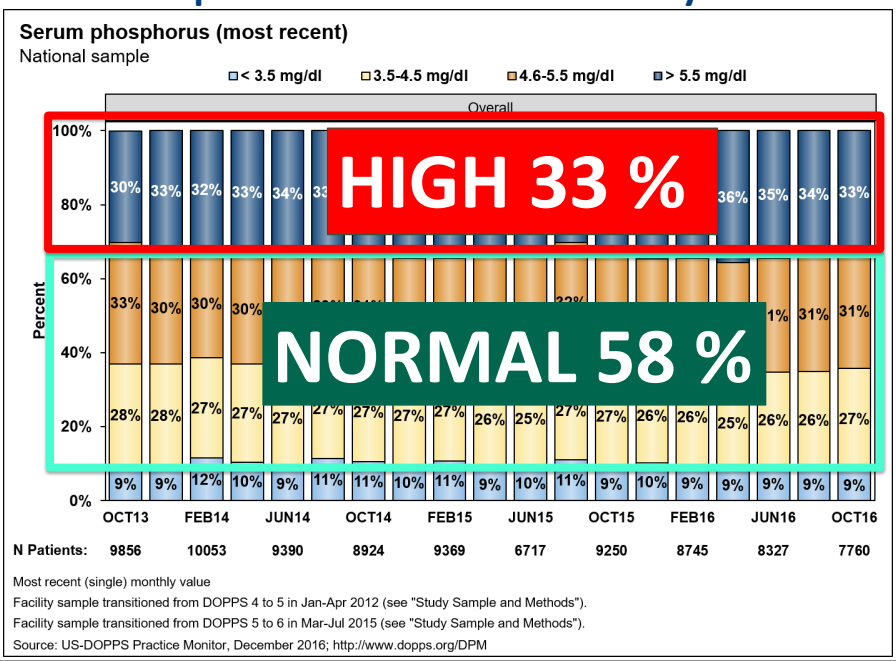
Serum Phosphate Concentration in Dialysis Patients



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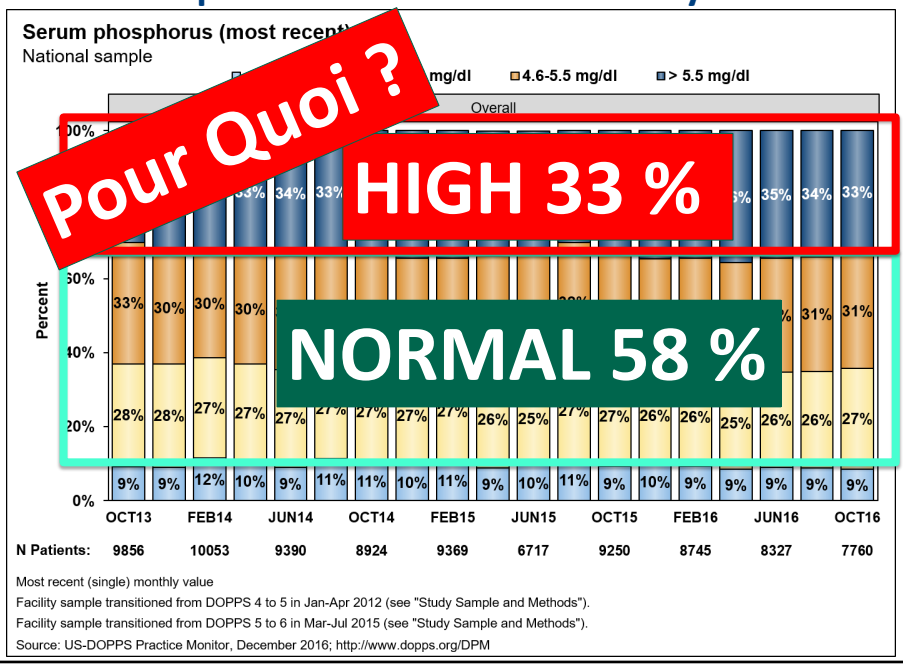
Serum Phosphate Concentration in Dialysis Patients



Pour Quoi ?

HIGH 33 %

NORMAL 58 %

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Principles for the Treatment of Hyperphosphatemia in CKD

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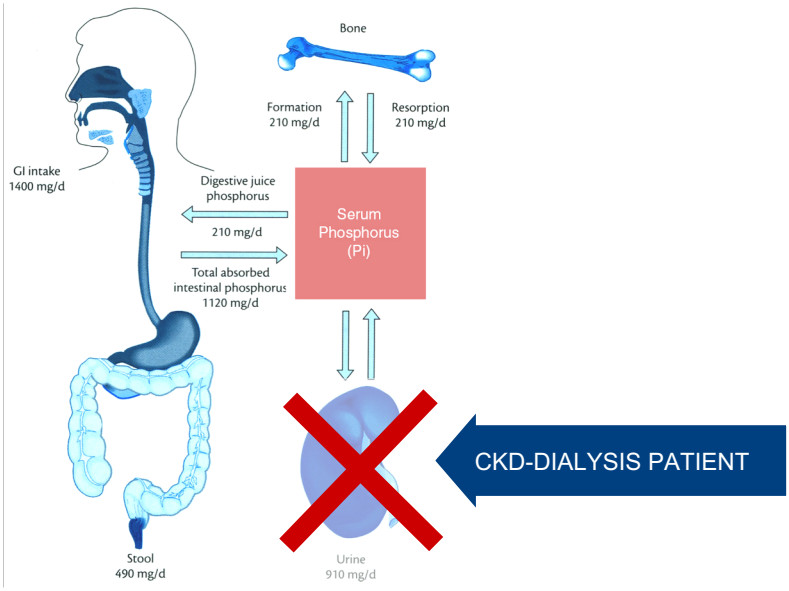
Phosphate Metabolism in Dialysis Patients



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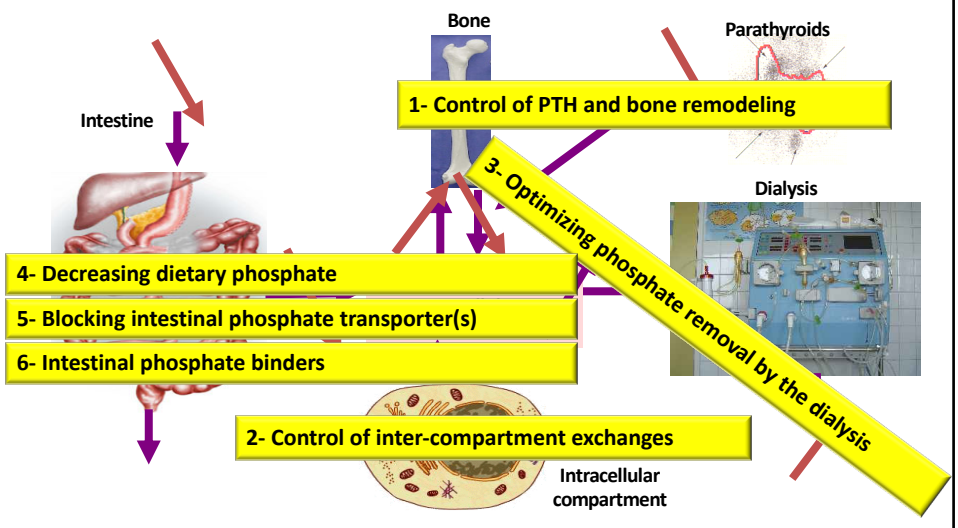
Principles for the Treatment of Hyperphosphatemia



- 1 - T. Drüeke & B. Lacour, in Comprehensive Clinical Nephrology, Feehaly, Floege and Johnson, Mosby Elsevier, Philadelphia, 3rd edition, pp 123-140-E.A.
- 2 - Clinical practice guideline. National Kidney Foundation. Am J Kidney Dis, 2003;42(4 Suppl 3):S1-201. K/DOQI clinical practice guidelines for bone metabolism and disease in chronic kidney disease.
- 3 – Ureña Torres P (sous la direction). Hyperphosphatémie dans l'insuffisance rénale chronique. J. Libbey Eurotext, Paris, 2004.
- 4 – Nissenson AR. Handbook of dialysis therapy, 4th edition. Saunders Elservier. 2008

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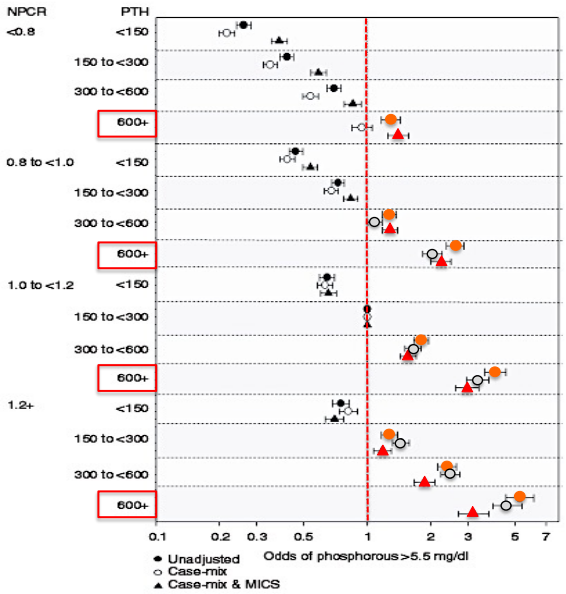
1- Control of PTH and bone remodeling

69,355 patients From the DaVita Database



Streja E et al. *Kidney Int Suppl* 3:462-468, 2015

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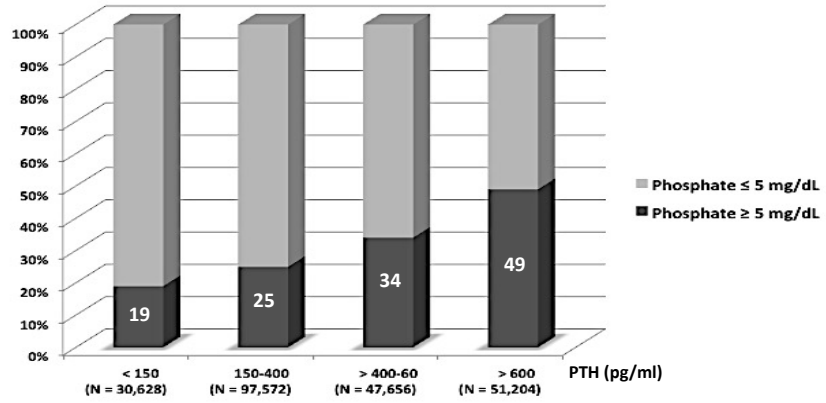
1- Control of PTH and bone remodeling

Increasing Serum PTH Levels Were Associated with a Higher Incidence of Elevated Serum Phosphate Levels (OutcomesPlus)



iPTH = Intact PTH.
Deidentified patient data from large and small dialysis organizations are shared with Amgen each month per contractual agreement. These data are reported cross-sectionally and form a report known as OutcomesPlus. OutcomesPlus database began in 2004. Data pulled monthly. Total N varies. Data from a subset of patients (N = 227,060) between August 24, 2014, and August 30, 2014, who had PTH, phosphorus, and calcium laboratory levels available and an average calcium level > 8.4 mg/dL. Because of patient switching between dialysis organizations, some duplication in patient count may occur.
Data on file, Amgen; [OutcomesPlus database; October 2014].

Data on file AMGEN 2015

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1- Control of PTH and bone remodeling

PTX
Calcimimétiques
Calcitonine
Bisphosphonates
Anti-RANKL

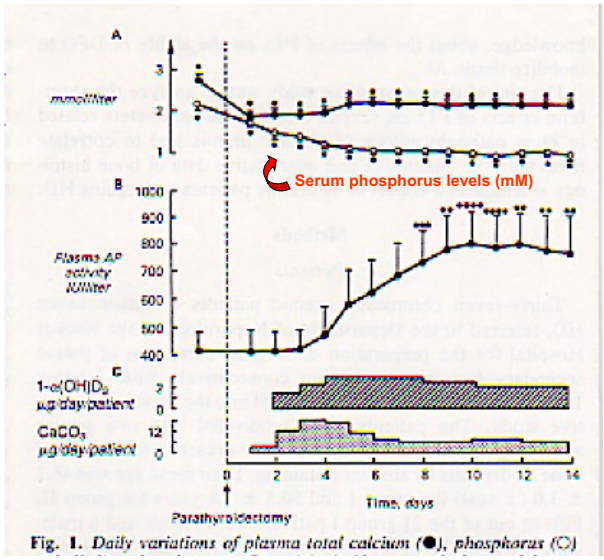

Fig. 1. *Daily variations of plasma total calcium (●), phosphorus (○)*

Urena P, et al. *Kidney Int* 36:120-126, 1989

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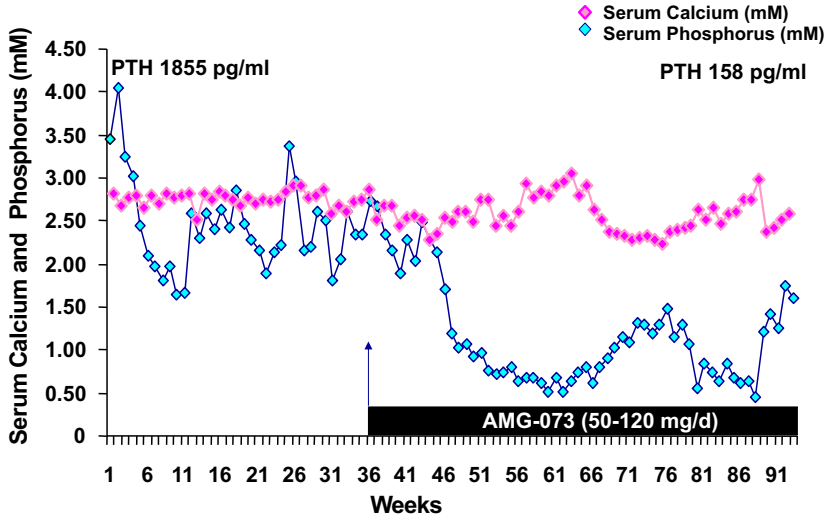
1- Control of PTH and bone remodeling

Calcimimetic Effects on Serum Calcium and Phosphate



Urena P et al. Orangerie data 2008 (COH)

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2- Control of inter-compartment exchanges

- Correction of acido-cetosis states
- Hormones: insulin, agonists b-adrenergics, cathecholamines, cortisol
- Renutrition syndrome

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3- Optimizing Phosphate Removal by the Dialysis

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Removal of Phosphate by Peritoneal Dialysis

TABLE I Mass phosphate removal in continuous ambulatory peritoneal dialysis (CAPD) and automated peritoneal dialysis (APD)

	Phosphate clearance (mg/wk)	
Reference	*APD*	*CAPD*
Messa *et al.* (3)		2028±1257 (*n*=35; 4×2 L) ~2941 (*n*=35, 4×3 L)
Evenepoel *et al.* (9)	2739±1042 (*n*=34)	2790±1022 (*n*=16)
Delmez *et al.* (10)		2170 (4×2 L)
Winchester *et al.* (11)		3250 (4×3 L)
Ketteler *et al.* (12)	2100–2800	
Botelho *et al.* (13)	3024 (renal plus peritoneal), 1862 (peritoneal alone)	

2,714 mg per week

Sawin DA. Advance in Peritoneal Dialysis 28:120-125, 2012

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Hémodialyse Conventionnelle

30 à 40 mmol/séance de dialyse (930 à 1240 mg)

Peu d'évolution depuis 10 ans

30% de la massa totale est transférée la 1ère heure

Peu de changement en fonction du dialyseur

- **Chauveau 1991 : 30-33 mmol/séance**
- **Gutzwiller 2002 : 30-32 mmol/séance**
- **Gotch 2003 : 30-34 mmol/séance**

28% de la variation de la masse de phosphate soustraite est expliquée par le Kt/V

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Cinétique de la Phosphatémie Pendant une séance d'Hémodialyse

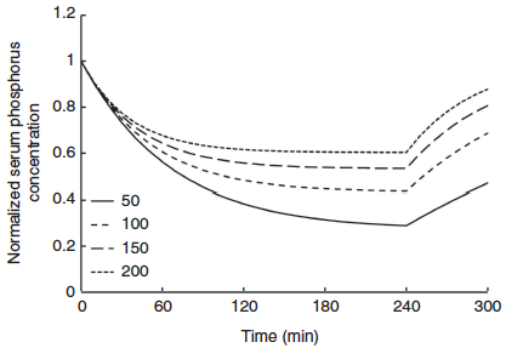

Figure 1 | Schematic demonstration of the effect of phosphorus mobilization clearance (K_M) on intradialysis and postdialysis serum phosphorus concentration normalized by its initial value. Different curves are plotted for different values of K_M as indicated; all other parameters were constant. The hemodialysis treatment time is assumed to be 240 min.

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Influence de la Durée de Dialyse sur la Quantité de Phosphate Eliminée

Table 2. Efficacy parameters of small solutes and the middle molecule β_2M during the 4- and 8-h dialysis sessions

	4 h	8 h	% increase (8 h vs 4 h)	P*
Total solute removal (mg)				
Urea	31 248 (12 239)	38 299 (17 132)	22.6	<0.003
Creatinine	1402 (685)	1750 (808)	24.8	<0.002
Uric acid	1135 (311)	1328 (310)	17.0	<0.002
Phosphorus	977 (218)	1237 (315)	26.6	<0.001
β_2M	181 (76)	252 (105)	39.2	<0.005

4 h, 350 ml/min vs 8 h 190 ml/min de débit sang et bain. Extraction + 39%
Basile et col. NDT 2011

4 h vs 8 h à Kt/V identique (1.3) : + 40%
Sampaio, Am J Nephrol 2012

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Influence de la Surface de la Membrane de Dialyse sur la Quantité de Phosphate Eliminée

Table 3. Phosphate Clearance and Phosphate Removal by Dialytic Regimen

Characteristic	Phosphate Clearance (mL/min)	Phosphate Removal (mg)
Standard hemodialysis	83.9 (71.6-96.2)	1,395.8 (1,163.6-1,628.1)
Increased dialysis time	86.6 (73.8-99.3)	1,435.7 (1,179.9-1,691.5)
Increased dialysate flow	83.0 (71.1-94.9)	1,371.4 (1,132.0-1,610.7)
2 Dialyzers in parallel	113.4 (101.4-125.3)	1,487.8 (1,248.6-1,727.1)

Note: N = 18. Values expressed as mean (95% confidence interval). Adjusted for rolling baseline serum phosphate level. Serum phosphate expressed in mg/dL; conversion factor for mmol/L, ×0.3229.

La dialysance n'augmente pas le transfert de masse

4h vs 4h30 vs dialysat 800 vs 2 dialyseurs (PS F80)
45 mmol -> 48 mmol

Tonelli et col. AJKD dec 09

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Influence de la Fréquence de la Dialyse sur la Quantité de Phosphate Eliminée: Dialyse Quotidienne

Gallan (SN, Tunis 2002)

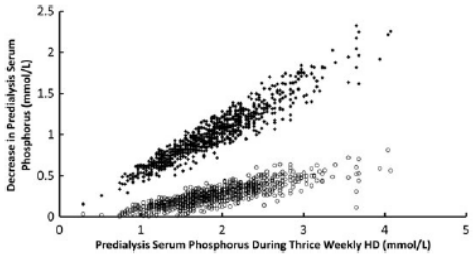
- Tf Masse 100 -> 128 mmol/sem + 30%
- Apports 968 -> 1535 mg/j + 58%

Lindsay (AM J Kid Dis, 2003)

- Ph T0: 5.6 ± 1.6 T12: 5.3 ± 1.3 mmol/l
- CaCO3 T0: 5.3 ± 6.3 T12: 3 ± 3 g / j
- Pas différent de la dialyse 3 jours/sem

Gotch-Levin (Blood Purif 2003)

- Tf Masse 121 vs 146 mmol / sem + 21%
- Apports 627 -> 989 mg/j + 58%
- Chélateurs 5 vs 14 cp / jour



Augmentation de l'extraction / semaine… mais augmentation des apports

Leypoldt J. NDT 2014

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Hémodialyse versus HDF Hemodiafiltration : Las Avis Sont Partagés

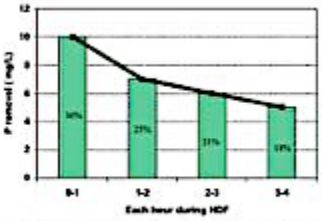

Figure 1. Mean P removal in spent dialysate and ultrafiltrate, collected hourly during a 4-hour HDF session. P, inorganic phosphorus; HDF, hemodiafiltration.

22 patients, 3x4 heures, cross-over

HD: 962 ± 312 mg vs

HDF: 1159 ± 296

Collection horaire du dialysat

Lornoy, JREN 2006

RESEARCH ARTICLE Open Access

Online-haemodiafiltration vs. conventional haemodialysis: a cross-over study

Cross-over 3x4 h, 6 mois

HDF-HD-HDF

Baisse de ß2m et Albumine

Pas de différence de phosphatémie

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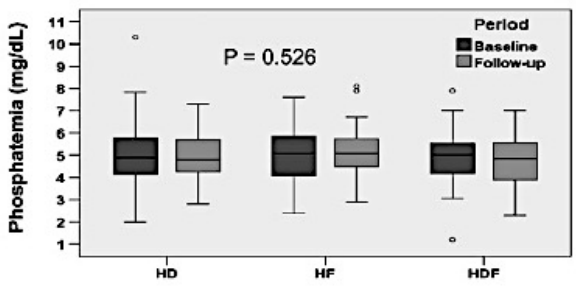
Hémodialyse versus Hemodiafiltration (HDF)

Nephrol Dial Transplant (2014) 0: 1–8
doi: 10.1093/ndt/gfu031

ndt Nephrology Dialysis Transplantation

Original Article

Phosphate levels in patients treated with low-flux haemodialysis, pre-dilution haemofiltration and haemodiafiltration: *post hoc* analysis of a multicentre, randomized and controlled trial



Locatelli F. NDT 2014

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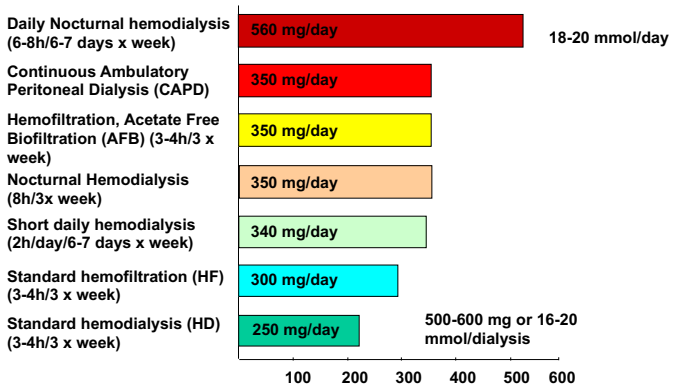
3- Optimizing phosphate removal by the dialysis



Diet Protein Intake	Phosphate content
1.1 to 1.4 g/kg/day	12 to 17 mg/kg/day
77 to 98 g/day (h-70 kg)	840 to 1190 mg/day
	5880 to 8330 mg/week
Intestinal absorption 60-70%	3480 to 4980 mg/week
Dialysis phosphate removal	1750 to 2350 mg/week
Positive balance	1730 to 3230 mg/week

Standard dialysis removes 20-30 mmol of PO_4 (620-930 mg/dialysis or 1860-2790 mg/week)

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Réduire les Apports Alimentaires et l'Absorption Intestinale de Phosphate

1- (4) Limiter les apports en phosphate tout en assurant une ration protéique et des apports caloriques suffisants

2- (5) Diminuer directement l'activité des transporteurs intestinaux de phosphate et ainsi l'absorption intestinale de phosphate

3- (6) Modulation du régime avec un chélateur du phosphate pris lors du repas

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Réduire les Apports Alimentaires et l'Absorption Intestinale de Phosphate

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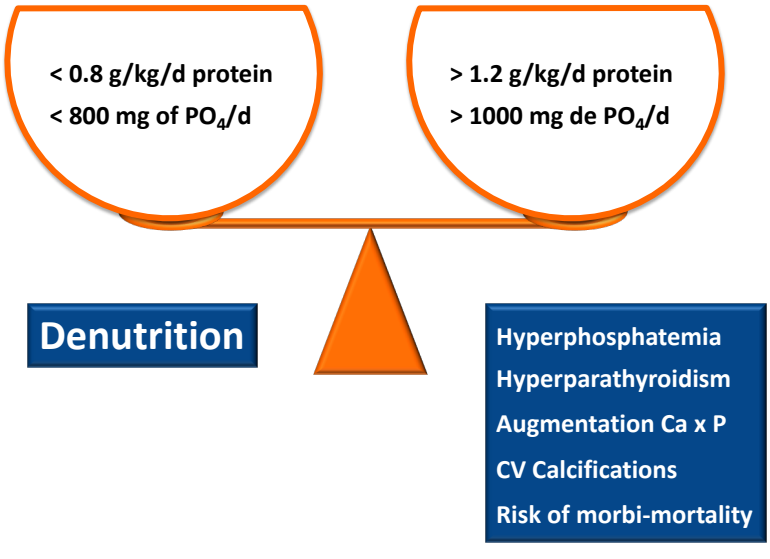
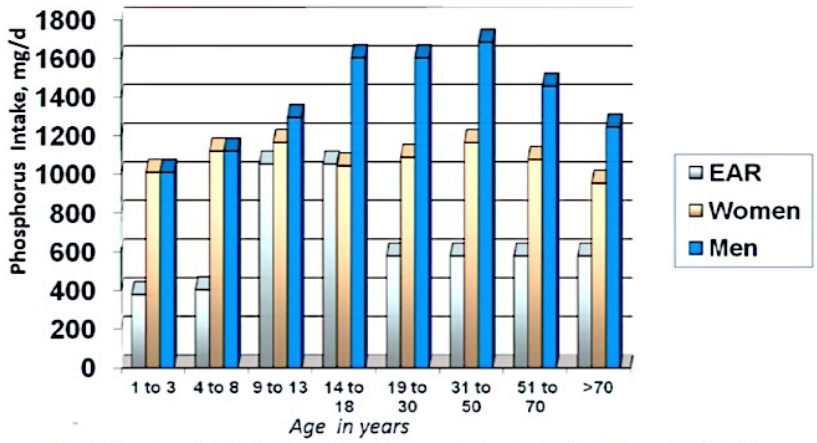
4- Decreasing dietary phosphate



49

NHANES 2005-2006 Usual Median Intake of Phosphate from Food Relative to the Estimated Average Requirement (EAR)



Source of data: US Department of Agriculture, Agricultural Research Service, Beltsville Human Nutrition Research Center, Food Surveys Research Group http://www.ars.usda.gov/ba/bhnrc/fsrg

Calvo MS, Uribarri J. Am J Clin Nutr 98:6, 2013

50

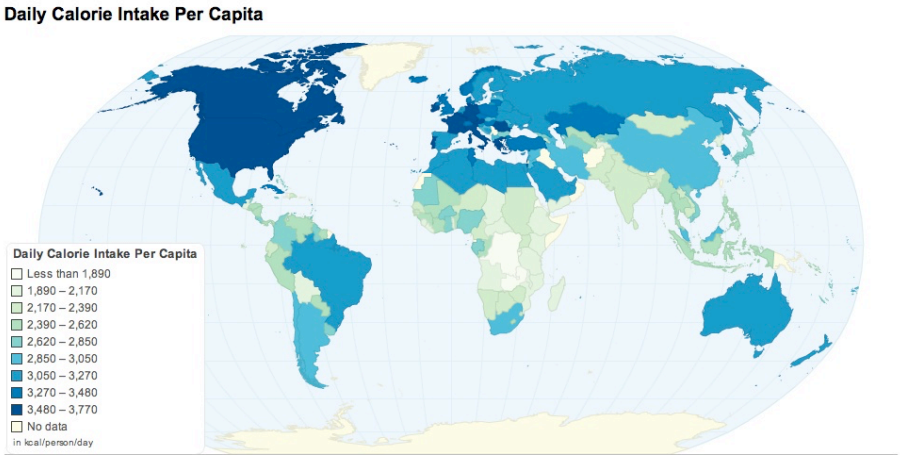
European Usual Daily Phosphate Intake

Country	Population	Number	Method	Mean (mg/day)	97.5 percentile
Italy	Household	2374	7-day record	1304	2076
Germany	Individual (Men) Individual (Women)	862 1144	7-day record + food frequency record	1488 1188	2517 1968
Netherlands	Household	5958	2-day record	1480	2601
Sweden	Individual (Men) Individual (Women)	1214	7-day record	1570 1290	2517 1968
United Kingdom	Individual (Men) Individual (Women)	656 803	7-day record	1493 1112	2381 1763

European Food Safety Authority, 2006

51

Approximative Estimation of Daily Phosphate Intake Worldwide



As low as 10-40 g of protein/day - 130- 520 mg/day of phosphate
As high as : 85-300 g of protein/day - 1200-4000 mg/day of phosphate

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Type of Phosphates in Nutrients

Organic

Plant derived

- Low absorption rate
- Approximately 40 % absorption efficiency
- Can interfere with the absorption of Ca, Mg Fe and Zn
- Only bioavailable after digested or degraded by phytase

Animal derived

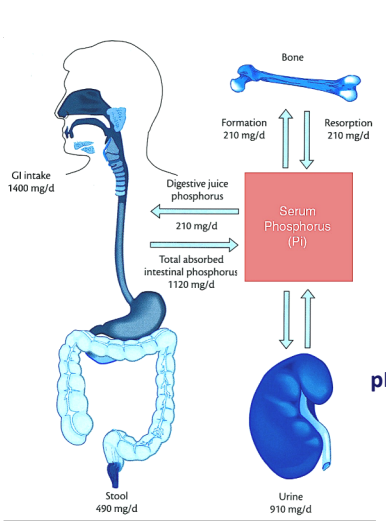
- Slightly faster absorption rate
- Approximately 40-60 % absorption efficiency
- No interference with the absorption of Ca, Mg or Zn
- Does not require special enzymatic digestion

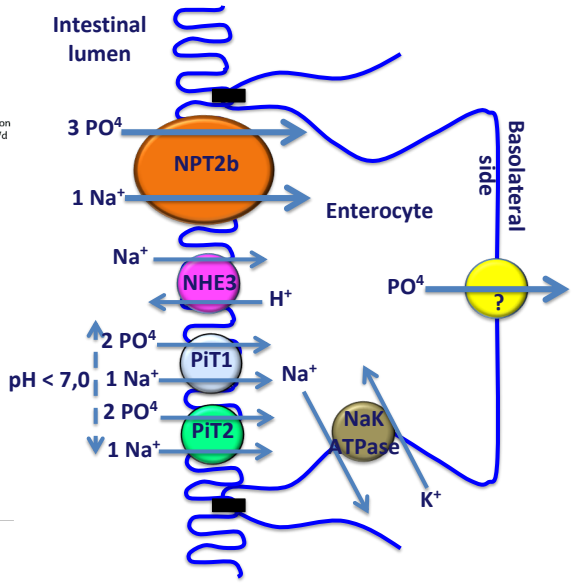
Inorganic

- Rapidly absorbed Approximately 70-100 %
- Highly bioavailable
- Rapidly dissociates in gut acidity
- Does not require special enzymatic digestion
- Some phosphate additives can be a major source of Na, Ca or Mg

53

Intestinal Absorption of Phosphate





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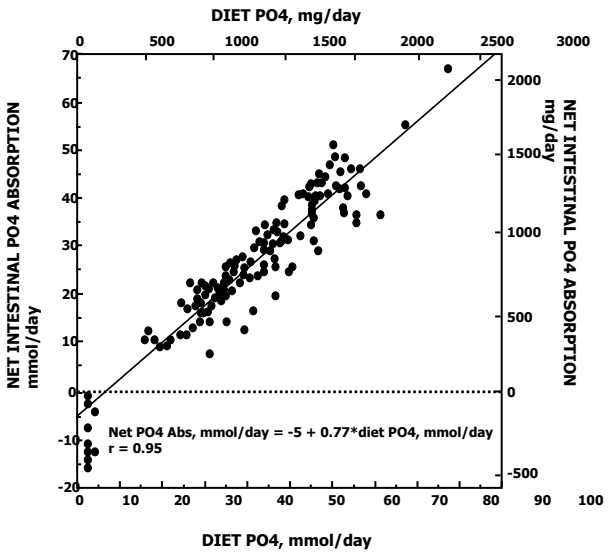
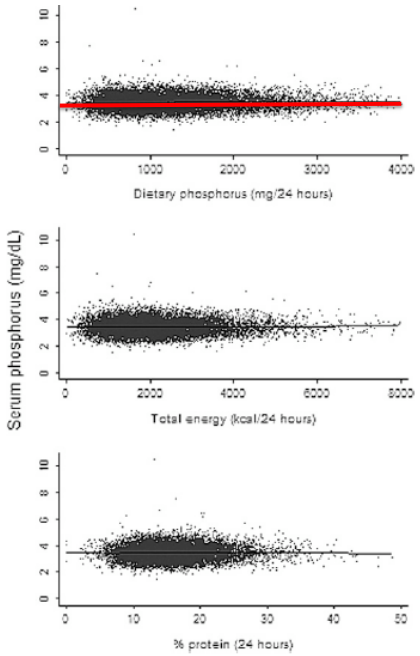
Intestinal Phosphate Absorption



Lemann J and Favus M, Primer JBMR 1999

55

Phosphate Intake, Demography, Cardiovascular Risk Factors, and Kidney Function Explain Only 12% of Variation in Serum Phosphate Levels (NHANES III)



Reasons:
1- Underestimation of phosphate content in foods (hidden phosphate in additives)
2- Differences in phosphate bioavailability. Type of phosphates (plants versus animals derived phosphates)
3- The ratio calcium:phosphate in foods
4- Other factors presents in the intestine (Mg, Na, pH, binders, etc)
5- Diurnal and circadian variation of phosphatemia
6- Age, Race, Gender

15,513 subjects

De Boer IH, et al., AJKD 53:399-407, 2009

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Nutrients Containing the Highest Phosphate Amount

Product	Total phosphate/100 g (mg)
Baking powder	1300
Cheese (Fourme d'Ambert)	1040
Wheat germ	1030
Skimmed milk powder	925
Cheese (Parmesan)	810
Cheese Beaufort	793
Cocoa	693
Steak of Soya	674
Sardine in Oil	530

ConsoGlobe. France

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Animal Derived Phosphates. Nutrients with the Best and the Worst Protein:Phosphate Ratio

Product	Total P/100 g (mg)	Digestible P/100 g (mg)	Protein/100 g (mg)	Total-P-to-Protein Ratio (mg/g)	Digestible-P-to Protein Ratio (mg/g)	P Additives
Cheese spread (9% fat)	892	794	18	49.6	44.1	E452, E339
Cheese spread (22% fat)	755	772	19	39.7	40.6	E452, E339
Processed cheese (23% fat)	584	576	21	27.8	27.4	E452, E339
Milk (1.5% fat)	108	85	3.2	33.8	26.6	-
Processed sausage (18% fat)	210	224	9	23.3	24.9	E450, E451
Frankfurter pool (20% fat)	175	144	9.2	19.0	15.7	E450, E451
Raw pork steak	212	161	21.0	10.1	7.7	-
Raw chicken filet	229	191	23.0	10.0	8.3	-

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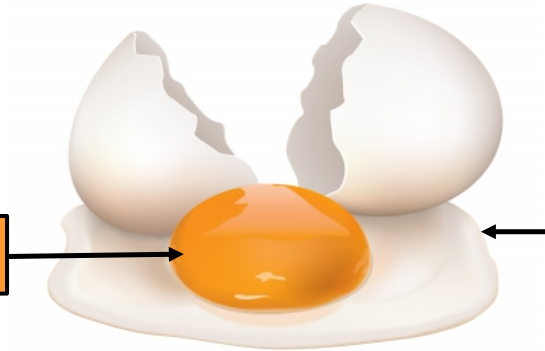
The Best Protein:Phosphate Ratio

Product	Total protein (g)	Digestible phosphate (mg)	Digestible-P-to Protein Ratio (mg/g)
Chicken egg			
Whole egg	12.4	210	16.9
Yolk egg	16.8	586	37.1
Egg white	10.9	15	1.4



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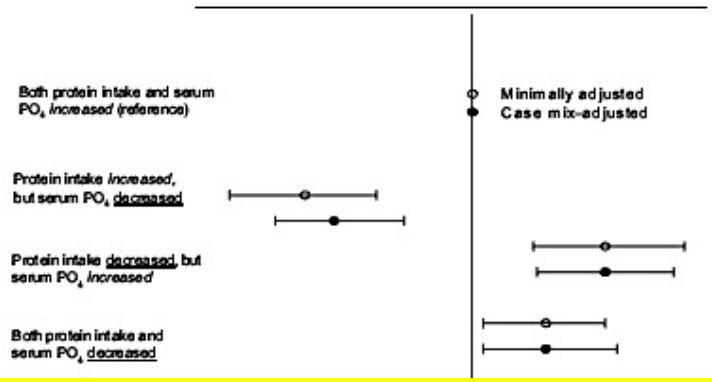
Is controlling phosphorus by decreasing dietary protein intake beneficial or harmful in persons with chronic kidney disease?



Conclusions: The risk of controlling serum phosphorus by restricting dietary protein intake may outweigh the benefit of controlled phosphorus and may lead to greater mortality. Additional studies including randomized controlled trials should examine whether nondietary control of phosphorus or restriction of nonprotein sources of phosphorus is safer and more effective.

Shinaberger C., et al., AJCN 88:1511-1518, 2008

65

Réduire les Apports Alimentaires et l'Absorption Intestinale de Phosphate

1- (4) Limiter les apports en phosphate tout en assurant une ration protéique et des apports caloriques suffisants

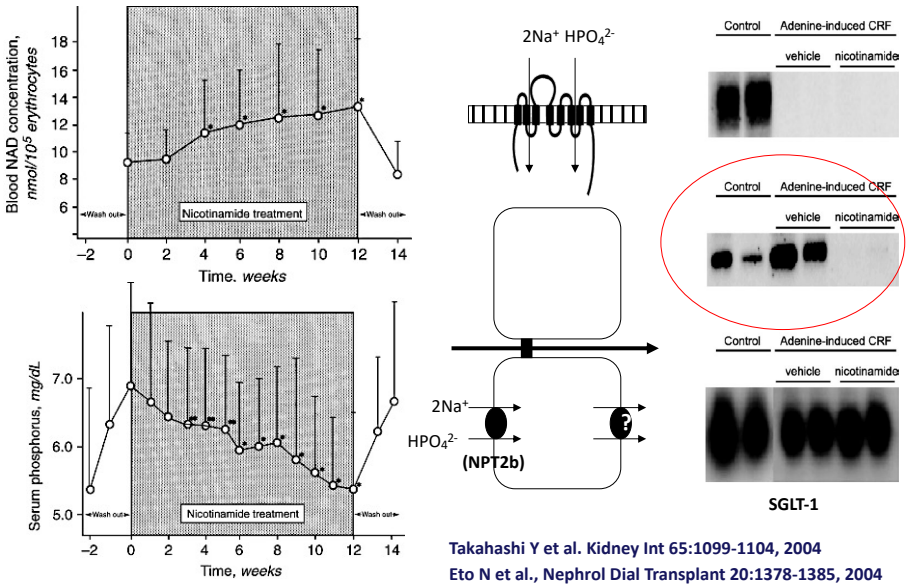
2- (5) Diminuer directement l'activité des transporteurs intestinaux de phosphate et ainsi l'absorption intestinale de phosphate

3- (6) Modulation du régime avec un chélateur du phosphate pris lors du repas

66

5- Blocking intestinal phosphate transporter(s)

Nicotinamide Decreases Serum Phosphate Concentration in Dialysis Patients



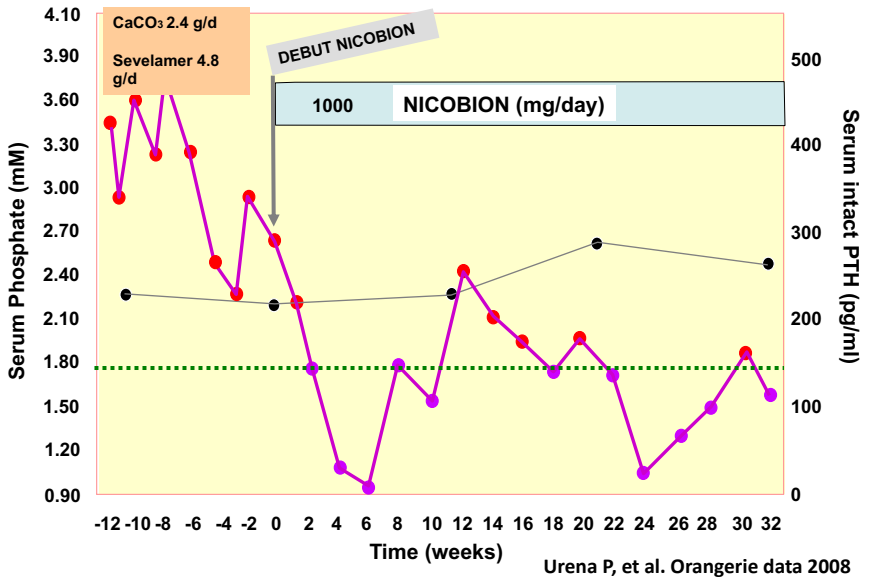
Takahashi Y et al. Kidney Int 65:1099-1104, 2004

Eto N et al., Nephrol Dial Transplant 20:1378-1385, 2004

67

5- Blocking intestinal phosphate transporter(s)

Serum Phosphate and PTH Concentrations in a Hemodialysis Patient Treated by Nicotinamide



Urena P, et al. Orangerie data 2008

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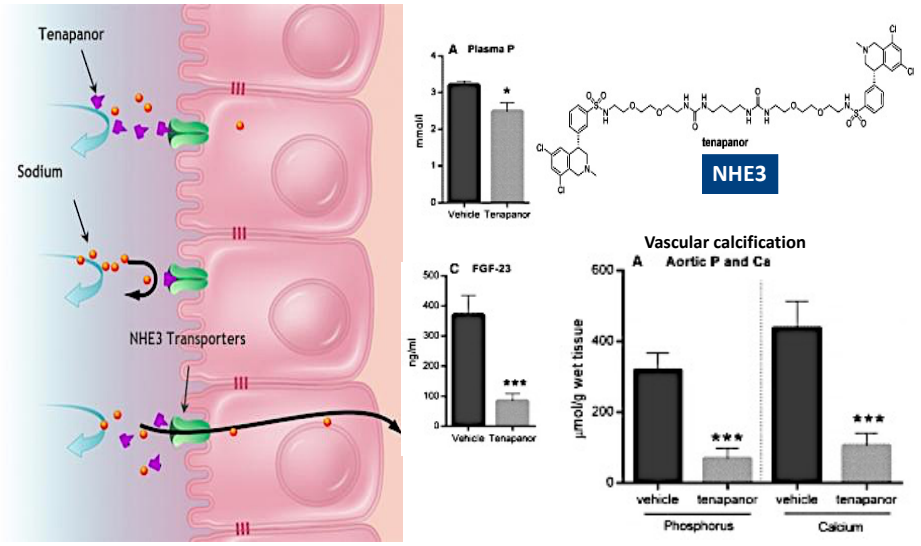
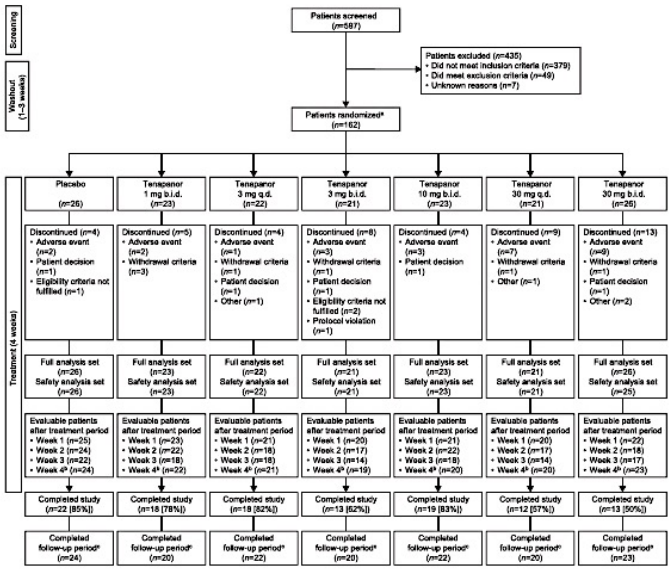
5- Blocking intestinal phosphate transporter(s)



Labonté E et al. JASN 26:1138-1149, 2015

70

5- Blocking intestinal phosphate transporter(s)



Block et al. CJASN 28, 2017

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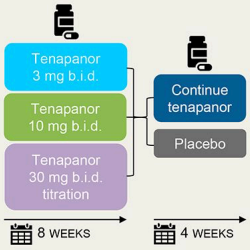
Tenapanor for Patients on Hemodialysis with Hyperphosphatemia: A Randomized Phase 3 Trial

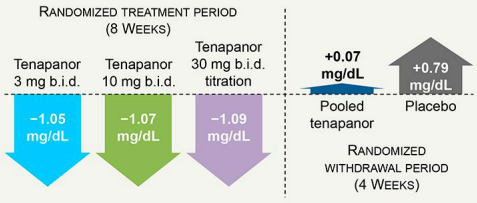
METHODS

219 patients across 41 US sites



RESULTS

Change in serum phosphate



CONCLUSION

Tenapanor significantly reduced elevated serum phosphate in patients on hemodialysis with hyperphosphatemia.

doi: 10.1681/ASN.2018080832

JASN
JOURNAL OF THE AMERICAN SOCIETY OF NEPHROLOGY

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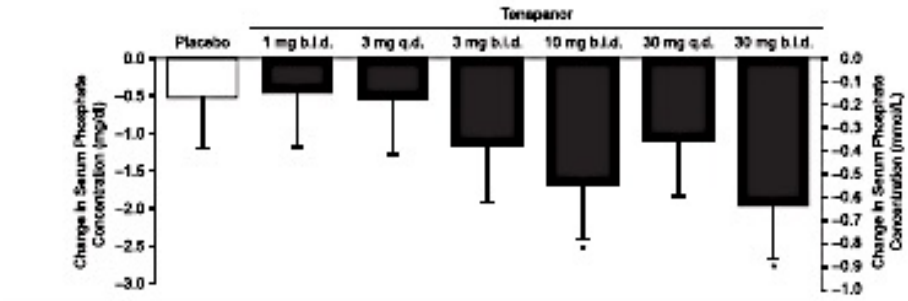
5- Blocking intestinal phosphate transporter(s)



Serum Phosphate Concentration (mg/dl)							
Baseline[a]	7.87±1.49	7.55±1.00	7.73±1.28	7.32±1.01	7.82±1.06	7.61±0.85	7.76±1.18
Change from Baseline at EOT/ET[b]	−0.54 (−1.21, 0.13)	−0.47 (−1.18, 0.24)	−0.56 (−1.28, 0.17)	−1.18 (−1.93, −0.44)	−1.70 (−2.41, −0.99)	−1.11 (−1.86, −0.37)	−1.98 (−2.67, −1.28)
n (baseline, EOT/ET)	26, 26	23, 23	22, 22	21, 21	23, 23	21, 21	25, 24

Block et al. CJASN 28, 2017

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Réduire les Apports Alimentaires et l'Absorption Intestinale de Phosphate

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6- Intestinal phosphate binders

Old and New Intestinal Phosphate Binders

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Types of Intestinal Phosphate Binders

1966	Carbonate de calcium	Avant 1980
1972	Hydroxyde d'alumine (1976 - encéphalopathie)	
1986	Carbonate de magnésium	
1986	Alginate de calcium	
1989	Acétate de calcium	1980 – 2000 (2003 K-DOQI)
1995	Chlorure de zirconyl	
1996	Kétoglutarate de calcium	
1999	Sulfate de fer hydrolysé	
2000	Sevelamer (Hydrochloride)	
2004	Carbonate de lanthane	Après 2009 (KDIGO)
2014	Sevelamer (Carbonate)	
2015	Ferric Citrate (JTT-751 ou Zerenex)	
2015	Sucroferric oxhydroxide ou PA21 (Velphoro)	
2015	Fermagate, SBR759, PT20 (iron-magnesium hydroxycarbonate)	

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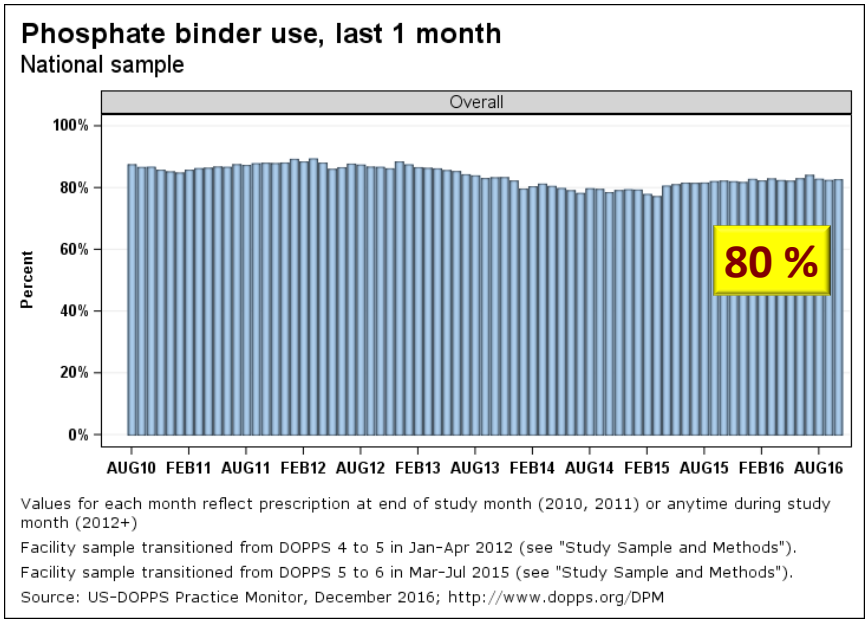
Prescription of Intestinal Phosphate Binders



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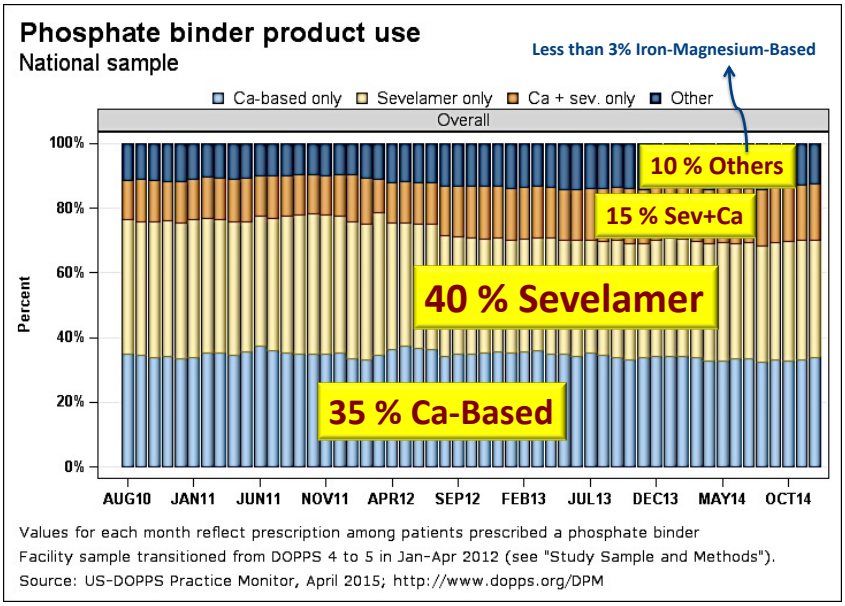
Prescription of Intestinal Phosphate Binders



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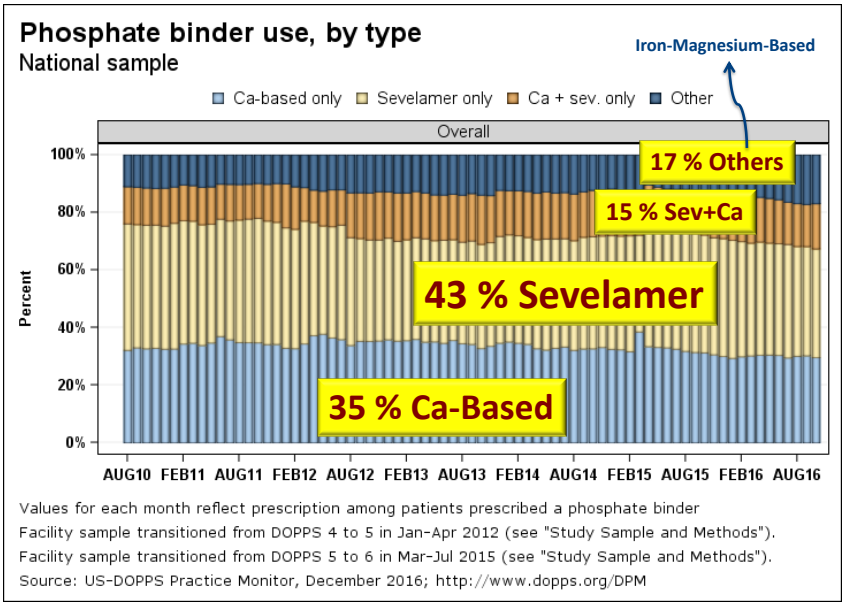
Prescription of Intestinal Phosphate Binders



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Mechanisms of Action of Intestinal Phosphate Binders

Nom	Contenu	Mode d'action
Calcium Acetate	253 mg of calcium element per 1000 mg of calcium acetate	Formation of insoluble calcium-phosphate complexes
Calcium Carbonate	400 mg of calcium element per 1000 mg of calcium carbonate	Formation of insoluble calcium-phosphate complexes
Sevelamer HCl		Ionic liaison and interaction between H+ and intestinal phosphate
Carbonate de sevelamer		Ionic liaison and interaction between H+ and intestinal phosphate
Lanthane Carbonate		Formation of insoluble lanthane phosphate complexes
Ferric Citrate	210 mg of ferric iron per 1000 mg of ferric citrate	Iron liaison with phosphate
Sucroferric oxyhydroxide	500 mg of iron per 2500 mg of Velphoro	Liaison of phosphate with the hydroxyle group and with water contained in Velphoro

Cada D. Hospit Pharm 50:139-151, 2015

80

Capacity of Intestinal Phosphate Binders

Name	Mg of phosphate/gramme of binder
Calcium Carbonate	43
Calcium Acetate	106
Aluminium Hydroxyde	150
Lanthanum Carbonate	156
Sevelamer Hydrochoride	140
Ferric Citrate	87
Sucroferric Oxyhydroxide	116

Adapted from Ureña P et al. John Libbey, 2004; Hsu CH et al. JASN 10:1274-1280, 1999; and FDA and EMA reports 2015.

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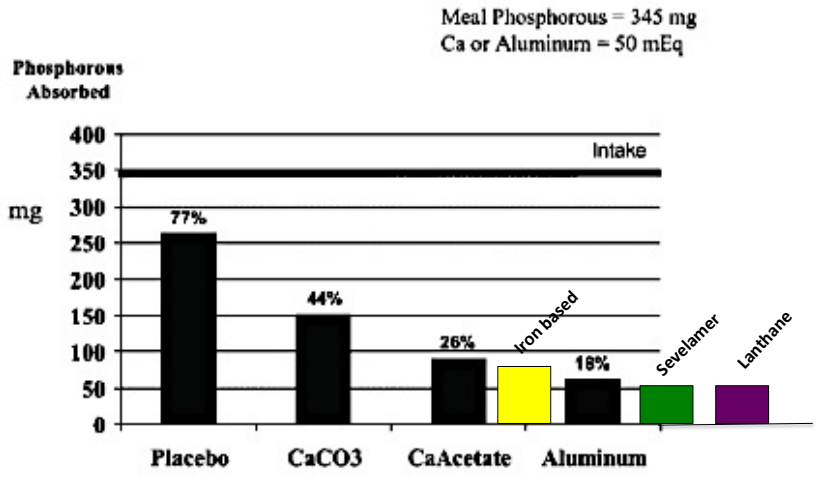
Capacity of Intestinal Phosphate Binders



Sheikh M et al. JCI 83:66-73, 1989

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Calcium-Based Intestinal Phosphate Binders

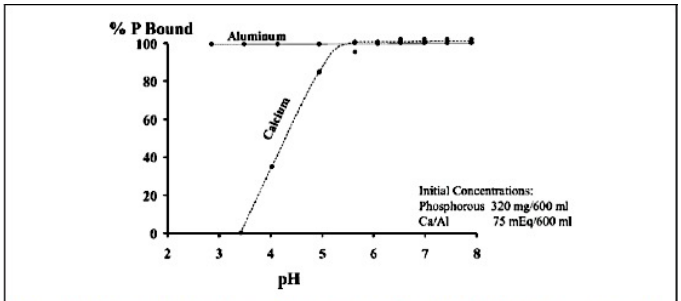

Figure 1. Theoretical analysis of the effect of pH on the binding of phosphorus by dissolved calcium or aluminum at equilibrium. Aluminum bound virtually all the phosphorus regardless of pH, whereas optimal calcium binding required a pH >5 (initial concentrations: phosphorous 320 mg/600 mL; calcium or aluminum 75 mEq/600 mL; adapted from Sheikh et al.).[25]

$CaCO_3$

An incongruous phosphate binder ?

Needs a low gastric pH in order to facilitate its dissolution and a high pH to bind phosphate, similar to other calcium salts

Sheikh M et al. JCI 83:66-73, 1989

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Calcium-Based versus Non-Calcium-Based Intestinal Phosphate Binders

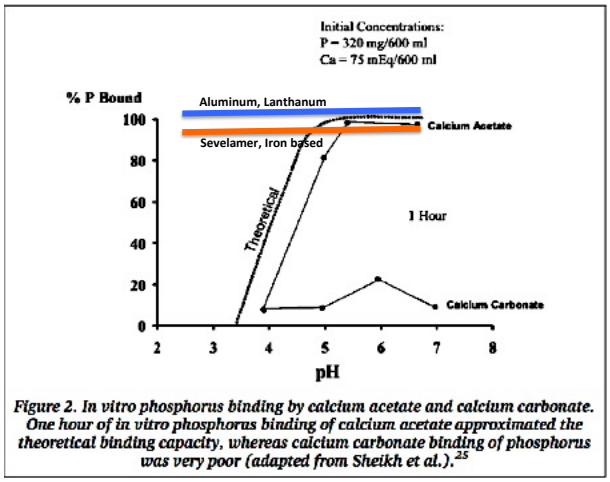


Figure 2. In vitro phosphorus binding by calcium acetate and calcium carbonate. One hour of in vitro phosphorus binding of calcium acetate approximated the theoretical binding capacity, whereas calcium carbonate binding of phosphorus was very poor (adapted from Sheikh et al.).[25]

Calcium Acetate

A more soluble calcium salt. 10 000 times more than CaCO3

Dissolution over a larger pH range than CaCO3

Maximal binding capacity obtained after one hour

Sheikh M et al. JCI 83:66-73, 1989

84

Calcium-Based Intestinal Phosphate Binders "Calcium Absorption"

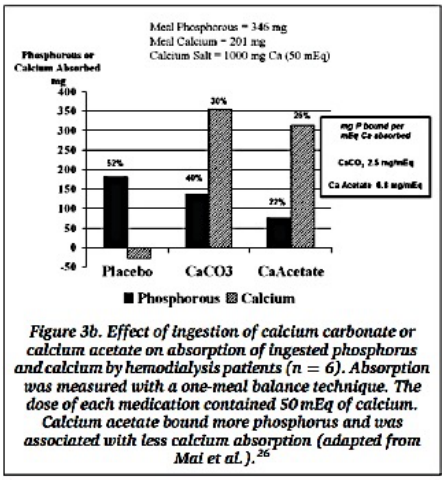
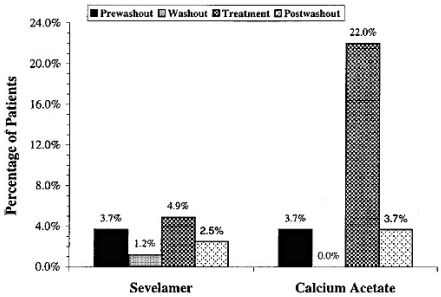


Figure 3b. Effect of ingestion of calcium carbonate or calcium acetate on absorption of ingested phosphorus and calcium by hemodialysis patients (n = 6). Absorption was measured with a one-meal balance technique. The dose of each medication contained 50 mEq of calcium. Calcium acetate bound more phosphorus and was associated with less calcium absorption (adapted from Mai et al.).[26]

Renagel vs Calcium Acetate: Less hypercalcemic episodes



A J. Bleyer et al. A Comparison of the Calcium-Free Phosphate Binder Sevelamer HydrochlorideWith Calcium Acetate in the Treatment of Hyperphosphatemia in Hemodialysis Patients. **Am J Kidney Dis Vol 33, No 4 (April), 1999: pp 694-701**

Mai MLet al. Kidney Int 36:690-695, 1989

85

7- Chélateurs de Phosphate

2009 : 4.1.5. Chez les patients avec MRC aux stades 3-5D et hyperphosphatémie, il est recommandé de restreindre la dose de chélateur du phosphate à base de calcium et/ou de vitamine D active s'il existe simultanément une hypercalcémie. Chez les patients avec MRC au stades 3-5D et hyperphosphatémie, il est recommandé de restreindre la dose de chélateur à base de calcium lorsqu'il s'il existe de calcifications artérielles et/ou une ostéopathie adynamique et/ou si la PTH est constamment basse.

2017 : 4.1.6. Chez les patients adultes avec MRC aux stades 3a-5D traités par chélateur intestinal du phosphate il est suggéré de restreindre la dose de chélateur à base de calcium (2B).

Argumentaire : *Il existe trois publications récentes des résultats d'études randomisées contrôlées appuyant cette notion quel que soit le stade de la MRC.*

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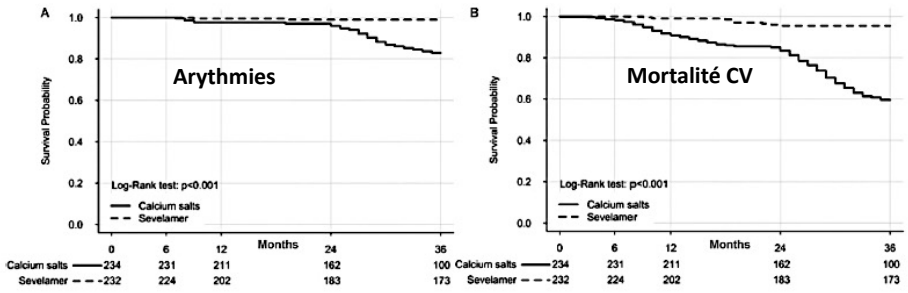
7- Chélateurs de Phosphate

Choix du Chélateur en Hémodialyse: L'étude INDEPENDENT

Population: 466 patients HD incidents
Intervention: Sevelamer
Comparateur: Chélateur à base de calcium
Critère principal: Décès dû à des arythmies cardiaques
Suivi: 36 mois (analyse après 24 mois)



Di Iorio B et al. AJKD 62:771-778, 2013

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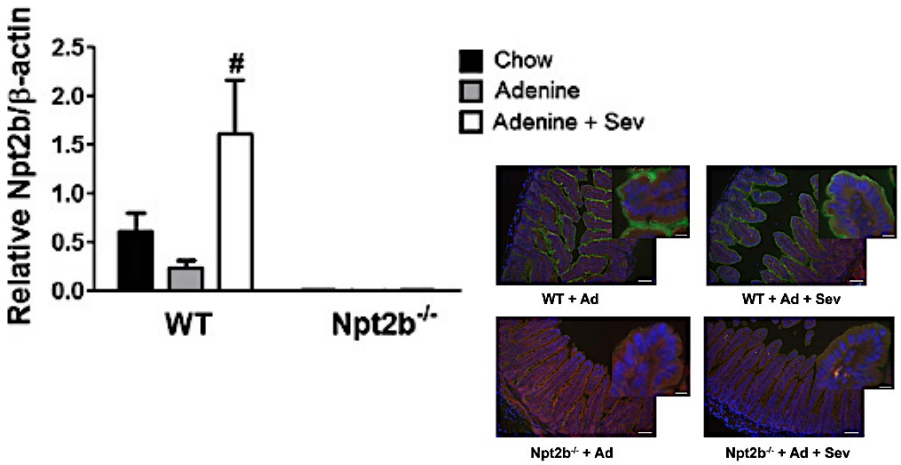
Effect of Phosphate Binders

Gastrointestinal Sodium Phosphate Cotransporter NPT2b ↑



Schiavi S et al: JASN 23: 1691-1700, 2012

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Effects of Intestinal Calcium-Based, Calcium-Free, and Iron-Based Phosphate Binders on Classical and Non Classical Biochemical Parameters (PO4, CRP, Uric Acid, FGF23)

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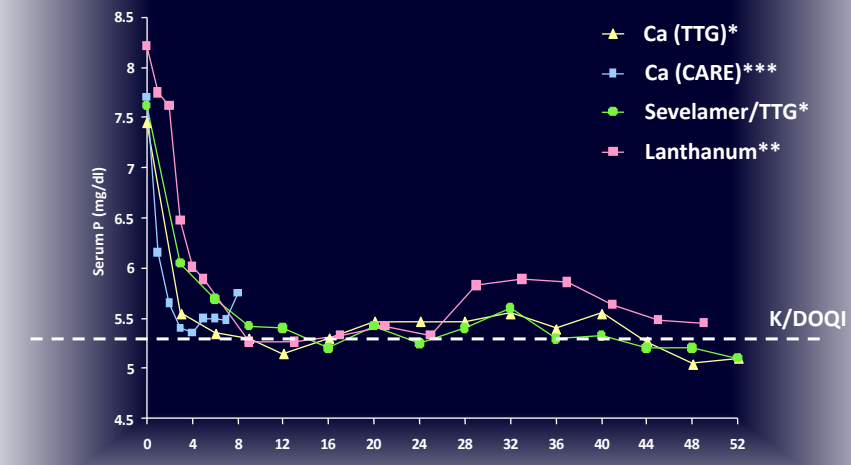
Efficacy of Phosphate Binders

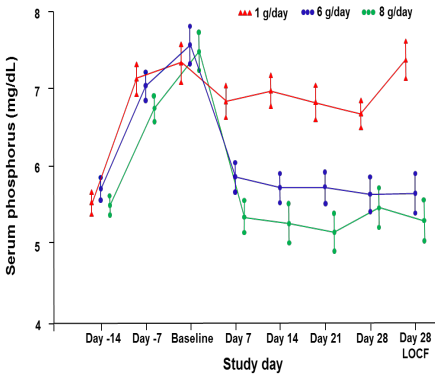


** TTG: Chertow GM. KI 2002*
*** Hutchison WCN 03. Berlin*
**** Qunibi W. Kidney Int. 2004 65: 1914*

90

Effect of Iron-Based Intestinal Phosphate Binders on Serum Phosphate Concentration

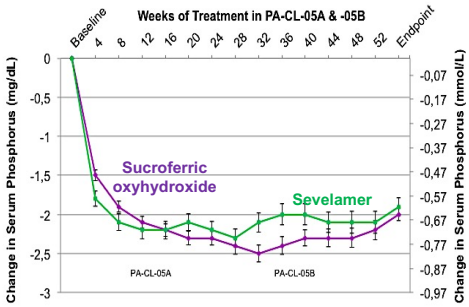
Ferric citrate



Ferric citrate
= 1,0 g (elemental iron content: 210 mg);
i.e. 6-8 tablets/day

Dwyer et al, Am J Kidney Dis 61: 759–766, 2013

Sucroferric Oxyhydroxide

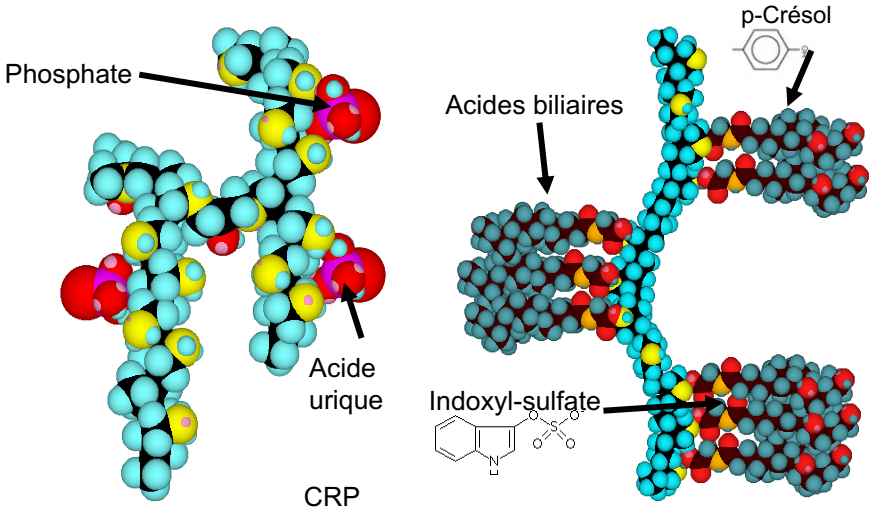


Sucroferric oxyhydroxide
= 500 mg (iron content: 500 mg (2.5 g tablet)
i.e. 3 tablets/day

Floege J et al, Kidney Int 2014

91

Autres Effets Biologiques des Chélateurs Non-Calciques (Sevelamer)



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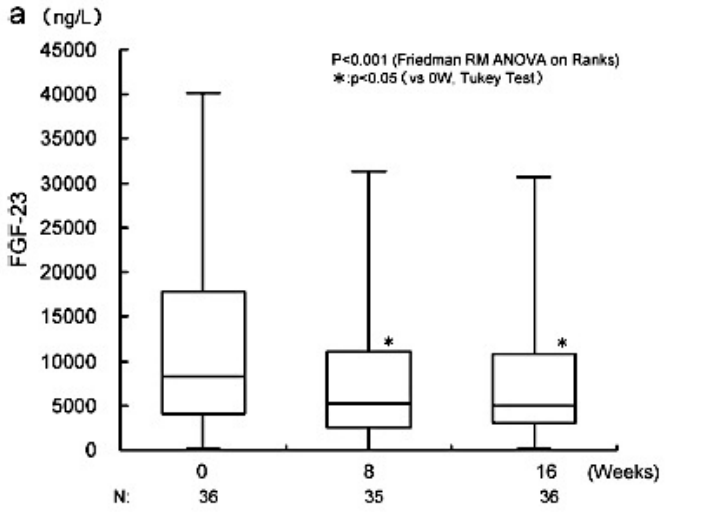
Combined therapy with lanthanum carbonate and calcium carbonate for hyperphosphatemia decreases serum FGF-23 level independently of calcium and PTH (COLC Study)



42 HD patients
PO4 > 6.0 mg/dL
CaCO3 add CaL
16 weeks

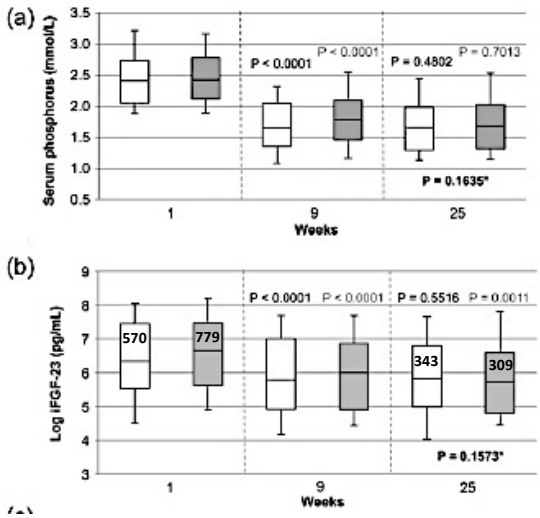
Shigematsu T et al. NDT 27:1050-1054, 2012

93

Calcium/Acetate Magnesium Carbonate versus Sevelamer HCl and the effect on serum FGF-23 levels (Post-hoc CALMAG study)

104 HD patients
105 CaMg
99 Sevelamer
25 weeks

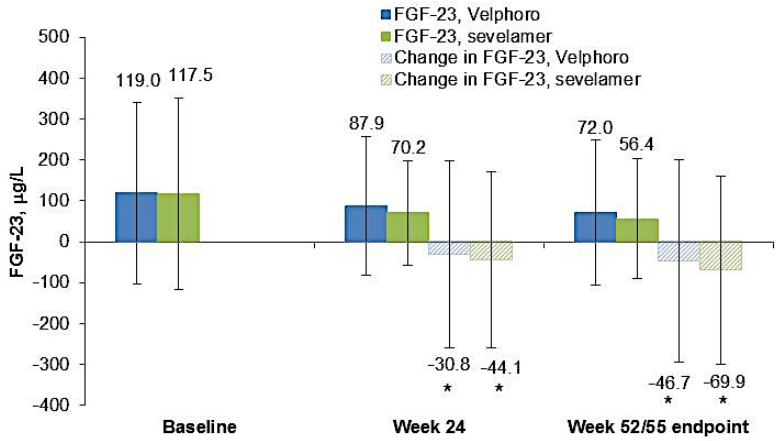
Both compounds
Significantly reduced
FGF23
No difference
Between groups



Covic A et al. NDT 28:2383-2392, 2013

94

Serum FGF-23 levels and Iron-Based Intestinal Phosphate Binder (Sucroferric Oxyhydroxide)



Decreases from baseline in mean serum FGF-23 concentrations were observed over 1 year in both Velphoro and sevelamer treatment groups. Integrated analysis of mean (SD) FGF-23 and change from baseline (SS; N=1,055) over 1 year.

Sprague SM et al. ASN 2013. Poster

96

Effects of Intestinal Calcium-Based, Calcium-Free, and Iron-Based Phosphate Binders on

Cardiovascular Calcifications

97

Coronary artery calcification (CAC): Randomized clinical trials comparing CaPBs and Sevelamer HCl

Study	Design	Results
Treat-to-Goal-Study (TTG) Chertow GM et al., KI 2002	▪ 200 patients, 1 year follow up ▪ Patients on sevelamer or any CaPB (CaAc or $CaCO_3$) ▪ PB doses to achieve sP and sCa target levels	▪ No difference in sP and Ca x P ▪ Significantly lower increase of CACS in Sevelamer pts ▪ Significant decrease in LDL and total cholesterol in sevelamer group
Renagel in New Dialysis (RIND) Block GA et al., KI 2005	▪ 129 incident HD pts, sevelamer or any CaPB for 18 months ▪ Management of parameters of bone metabolism at investigators' discretion	▪ Lower increase of CACS in sevelamer group ▪ Significant decrease in LDL and total cholesterol in sevelamer group
CARE II Qunibi et al, AJKD 2008	▪ 203 pts (52 weeks) on Ca Ac or Sevelamer, both + atorvastatin	▪ No difference in calcification ▪ No difference in LDL levels
BRiC Barreto et al., Nephrol Clin Pract 2008	▪ 71 pts, on Ca Ac or sevelamer for 12 months ▪ dCa and vit D regimen changes during study	▪ No difference in calcification ▪ No difference in bone turnover ▪ No difference in LDL levels

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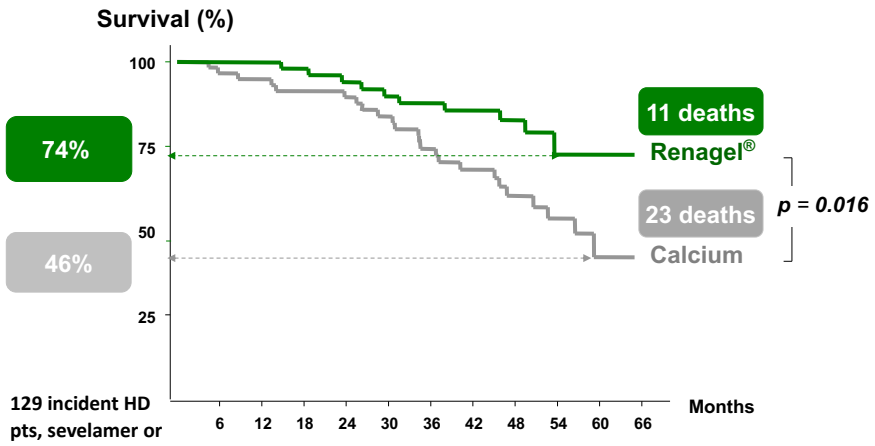
Effects of Intestinal Calcium-Based, Calcium-Free, and Iron-Based Phosphate Binders on

Mortality Risk

99

Effect of Sevelamer and Calcium-Based Intestinal Phosphates Binders on Survival in HD Patients "RIND Study"



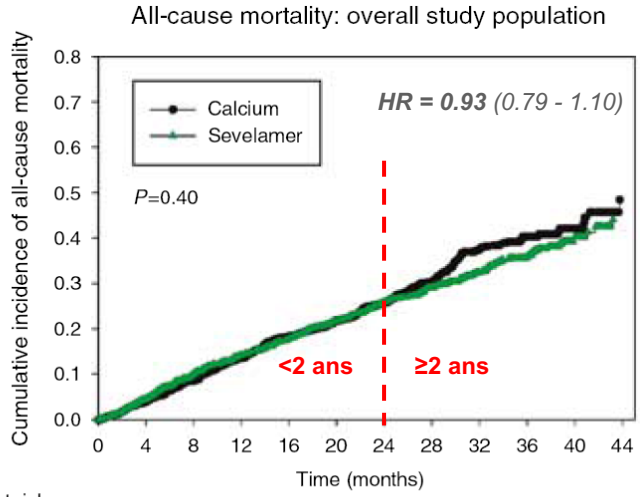
- 129 incident HD pts, sevelamer or any CaPB for 18 months

Block et al. Kidney Int 2007;71:438–441

100

Effect of Sevelamer and Calcium-Based Intestinal Phosphates Binders on Survival in HD Patients "DCOR Study"

- 2013 prevalent dialysis patients
- 1053 sevelamer
- 1050 any CaPB
- follow-up 2 years



Suki et al. Kidney Int.(2007) 72, 1130–1137.

101

Effect of Sevelamer and Calcium-Based Intestinal Phosphates Binders on Survival in HD Patients "DCOR Study"

- 2013 prevalent dialysis patients
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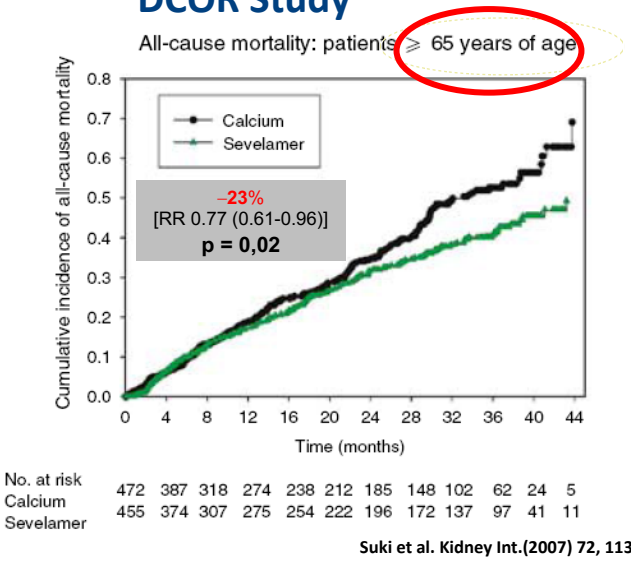

Suki et al. Kidney Int.(2007) 72, 1130–1137.

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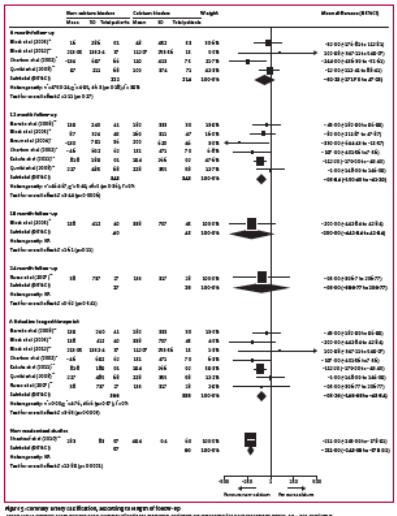
Effect of Sevelamer and Calcium-Based Intestinal Phosphats Binders on Survival in HD Patients



Meta-Analysis of
11 RCTs (4622 patients)
Patients assigned to non calcium-based phosphate binders had a 22% reduction in the risk of all-cause mortality compared with those assigned to calcium-based phosphate binders
(risk ratio 0·78, 95% CI 0·61–0·98)

Jamal S et al. Lancet 382:1268-1277, 2013

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Side Effects

of Intestinal Calcium-Based, Calcium-Free, and Iron-Based Phosphate Binders

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Tolerability contributes to non-adherence: common adverse events reported with phosphate binders

Drug	Adverse effects
Tums, Os-Cal, Caltrate (calcium carbonate) and Phoslo, Eliphos (calcium acetate)	**Gastrointestinal effects** in **22**% of patients; **hypercalcemia** in 10% of patients (12–54); **peritonitis** in 4% of patients; **pruritus** in 10% of patients; **xerostomia** in 12% of patients; **muscle cramping** in 6% of patients
Renagel (sevelamer hydrochloride) and Renvela (sevelamer carbonate)	**Gastrointestinal effects** in **38**% of patients; **hypercalcemia** in 13% of patients; **metabolic acidosis** in 34% of patients (*Renagel*); **peritonitis** in 11% of patients
Fosrenol (lanthanum carbonate)	**Peripheral edema** in 24% of patients; **gastrointestinal effects** in **8**% of patients; **hypercalcemia** in 6% of patients; **muscular cramping** in 7% of patients; **myalgia** in 21% of patients; **peritonitis** in 4% of patients

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K-DOQI and KDIGO Recommendations.

How can they help us to choose the type of intestinal phosphate binder?

106

6- Chélateurs de Phosphate

2009 : 4.1.4. Chez les patients avec MRC aux stades 3-5 (2D) et MCR-5D (2B), il est suggéré de traiter l'hyperphosphatémie par des chélateurs intestinaux du phosphate. Le choix du chélateur doit tenir compte du stade de la MRC, de la présence ou non d'autres composants de la MRC-TMO, des traitements concomitants et des effets indésirables des chélateurs.

2017 : 4.1.5. Chez les patients avec MRC aux stades 3a-5D, les décisions sur la stratégie thérapeutique visant à faire baisser la phosphatémie devrait être basée sur le caractère progressif et persistent de l'hyperphosphatémie (non gradé).

Argumentaire : *Cette recommandation souligne la perception, selon laquelle les mesures préventives très précoces contre l'hyperphosphatémie améliorerait le pronostic, n'est pas soutenue par des données scientifiques solides.*

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In Practice: How to Choose An Intestinal Phosphate Binder ?

1- Based on biochemical parameters (Calcemia, Phosphatemia and PTH)

2- Based on the presence or the absence of cardiovascular calcifications

~~3- Based on the bone biopsy data (presence or the absence of bone turnover or an adynamic bone disease)~~

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In Practice: How to Choose An Intestinal Phosphate Binder ?

	Calcemia	Vascular Calcifications	Ca-Based Phosphate Binder	Ca-Free Phosphate Binder
PTH Normal/ Low	N/Low	YES		+
		NO	+	+/-
	High	YES		+
		NO		+
PTH High	N/Low	YES	+/-	+/-
		NO	+	
	High	YES		+
		NO		+

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Cost of Intestinal Phosphate Binders

Name	Dose Range	Cost per month (€)
Calcium Acetate	Variable	11 - 34
Calcium Carbonate	Variable	11 - 25
Calcium Acetate/Magnesium Carbonate (Osvaren)	3-10 Tablets	15-55
Aluminum Hydroxyde	4-20 Capsules	18 - 90
Sevelamer HC (Renagel)	1-5 Tablets 3 times a day	110 - 550
Sevelamer Carbonate (Renvela)	1-3 Tablets 3 times a day	110 - 330
Lanthanum Carbonate (Fosrenol)	1,500-3,000 mg per day	163 - 254
Sucroferric Oxohydroxide (Velphoro)	3-6 Tablets per day	235 - 471

Adapted and modified from Pennoyer A. Drug Foerecast 40:329-339, 2015

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THANK YOU VERY MUCH

MERCI BEAUCOUP

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